The most commonly used product was Recombinate, currently used by over half (55%) of the patients interviewed Kogenate was currently used by just under one quarter of patients (23%), Helixate by 14%, Refacto by 8% and Bioclate by 2%

Patients in all countries were using Recombinate, from one fifth of patients in Spain to all six patients in Denmark It was the most widely used rFVIII product in all countries except Spain where Kogenate was the leading brand A full breakdown by country can be found in the computer tabulations that accompany this report.

Not only was Recombinate currently the most commonly used rFVIII product, there had also been minimal switches away from Recombinate - only 6% of patients claimed to have used the product in the past It is interesting to compare this with the lower penetration products – Kogenate, where 15% had switched to a different product and Helixate (10% switches)

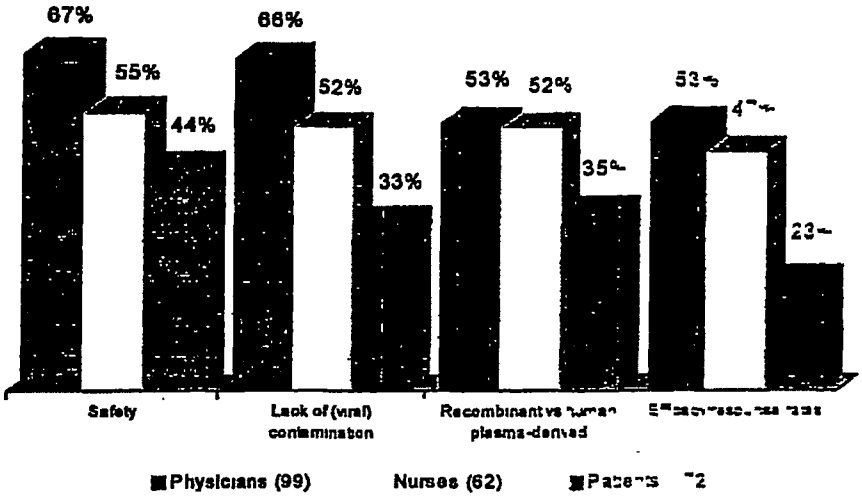
3.8 Influences on choice of product

A number of factors were said to influence the choice of Factor VIII product in the treatment of haemophilia A The most commonly mentioned factors for physicians nurses and patients related to minimising patient risk and included

- safety,
- minimal risk of viral contamination,
- the associated source of the product (genetically engineered or plasma-derived)

Efficacy/response rates was also a significant consideration for physicians and nurses, as were supply and cost (each mentioned by between 41% to 65% of these respondent groups)

Factors most influencing the choice of Factor VIII products



Base All physicians nurses and patients

Additional factors mentioned by at least one fifth of any single respondent group are included in the following table

Factor	Physicians (99)	Nurses (62)	Patients (172)
Lack of adverse reactions	40%	37%	16%
Lack of immunity / resistance / inhibitor development	34%	34%	0%
Ease of administration	29%	35%	18%
Albumin/protein content	28%	13%	10%
Ease of reconstitution	28%	34%	15%
Well-established product	28%	40%	*
Storage (refrigeration vs room temperature)	28%	15%	16%
Shelf-life	26%	16%	9%
Duration of effect	25%	35%	17%
Speed of response	23%	23%	22%
Range of potencies/vial sizes	20%	32%	9%
Diluent/infusion volume	19%	26%	8%
Speed of reconstitution	18%	26%	15%
Manufacturer (e g reputation or involvement in haemophilia)	11%	27%	0%
Delivery to patient's home	9%	23%	13%
Recommended by hospital/GP	n/a	n/a	22%

There were some variations in the responses between physicians, nurses and patients and it is interesting to note where the variances occur

- the associated source of the product (genetically engineered or plasma-derived) was mentioned by over half of the nurses (52%, and physicians (53%), and more than one third of patients (35%) Interestingly, the actual albumin/protein content of the product was a more influential issue to physicians – mentioned by over one quarter (28%) than for nurses (8%) or patients (10%),
- factors that could be associated with the task of administering the product as opposed to the manufacture/content of the product, appeared to be more influential for nurses, but less so for physicians and patients These included
  - supply/availability(65%, 51%, 5%* respectively),
    *patients were probed on availability only
  - ease of administration (35%, 29%, 18% respectively)
  - ease of reconstitution (34%, 28%, 15% respectively)
  - speed of reconstitution (26%, 18%, 15% respectively)
  - range of potencies/vial sizes (32%, 20%, 9% respectively)
  - diluent/infusion volume (26%, 19%, 8% respectively)
- the manufacturer was a factor that was more influential for nurses than for physicians (27% vs 11% respectively), as was whether the product was well-established or not (40% vs 28% respectively),
- more than one fifth of patients (22%) were influenced by a recommendation or choice of product by their GP or hospital This was the fifth most influential factor among patients,
- interestingly, storage and shelf-life were more influential factors for physicians (mentioned by more than 25%) than for nurses and patients

Nurses were not included in the sample in several European countries thus reducing the validity of the multivariate analysis for this respondent group To validate the nurses' conjoint analysis, they were asked to rate the level of importance of each of the factors included in the following table on a scale of one to ten, where one equalled 'not at all important' and ten equalled extremely important

	Factor	Mean rating
1	Lack of (viral) contamination	9 9
2	Safety	9 8
3	Lack of immunity/resistance/inhibitor development	9 5
4	Lack of adverse reactions	9 4
5	Efficacy/response rates	9 3
6	Recombinant vs human plasma-derived	9 2
6	Supply/availability	9 2
7	Speed of response	8 9
8	Duration of effect	8 7
8	Cost	8 7
9	Well established product	8 5
10	Ease of administration	8 4
11	Ease of reconstitution	8 3
11	Lack of albumin reaction	8 3
12	Speed of reconstitution	8 0
13	Range of potencies/vial sizes	7 8
14	Shelf-life	7 6
15	Diluent/infusion volume	7 4
16	Manufacturer (e g reputation)	7 3
17	Albumin/protein content	7 2
18	Storage (refrigeration vs room temp)	6 8
18	Good relationship with manufacturer	6 8
19	Delivery to patients home	6 5

There were some country variations in the importance ratings of the factors influencing the choice of Factor VIII treatment. With regard to the most influential factors, the variances were as follows

- efficacy/response rates achieved a mean rating of 7 5 in Japan (5 respondents) whereas the nurses in the other four countries awarded a mean rating of 8 6 or above,
- the recombinant vs human plasma-derived factor was rated 8 8 or above in all countries except for Sweden (5 respondents) where the mean rating was 7 8
- all the nurses except for those in Japan awarded supply availability a mean rating of 9 3 or above In Japan the mean rating was 7 2

There were also some interesting variances in the ratings for the other factors

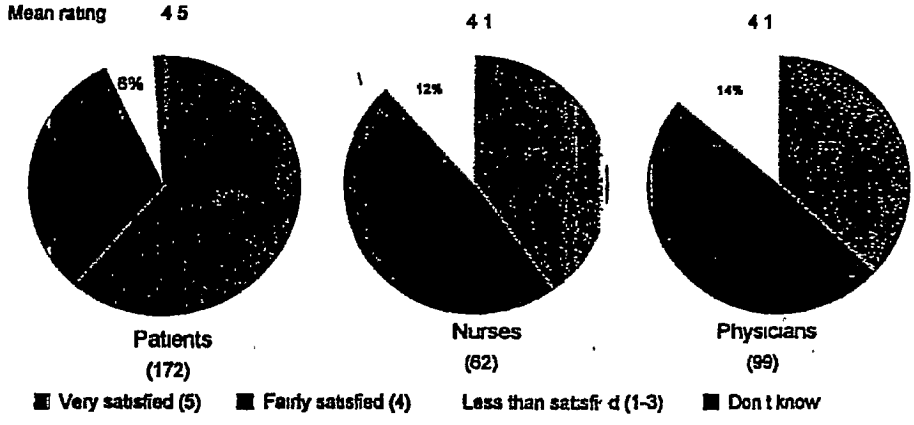
- nurses in all countries except Denmark (2 respondents) rated the well-established/standard product factor at 8 4 or above In Denmark the mean rating was 5 0,
- the albumin/protein content factor was rated as being more important in Denmark with a mean score of 9 0 as opposed to 7 0 - 7 7 in the other countries,
- Denmark (two respondents) showed a mean rating of 10 0 for eight factors - six of the seven most important factors among all nurses (no efficacy/response rates) plus speed of response and shelf-life, whereas the only other country to register a mean score of 10 0 was Sweden (five respondents) when rating risk of (viral) contamination,
- there was a wide range of ratings for diluent/infusion volume from 6 0 in Japan to 9 0 in Denmark,
- shelf-life was extremely important in Denmark (mean rating of 10 0) but of minimal importance in Japan (mean score 5 8) The other countries gave this factor a mean rating of 7 2 - 8 7,
- although the factor labelled 'delivery to patient's home' scored a mean rating of 6 5, it was considered of little importance in Denmark where it scored a mean rating of 1 0,

- having a good relationship with the manufacturer (mean rating of 6 8) was considered most important in the UK, with a mean score of 8 6, and the least important in Japan where it scored 5 8,
- cost (mean rating of 8 7) was highly ranked in all countries except Denmark, where it had a mean rating of 6 0

3.9 Level of satisfaction with current rFVIII products

All physicians, nurses and patients were asked to rate how satisfied they were with the rFVIII products currently available A five-point rating scale was used where one equalled very dissatisfied and five equalled very satisfied

Level of satisfaction with recombinant Factor VII products currently available (1 = very dissatisfied and 5 = very satisfied)

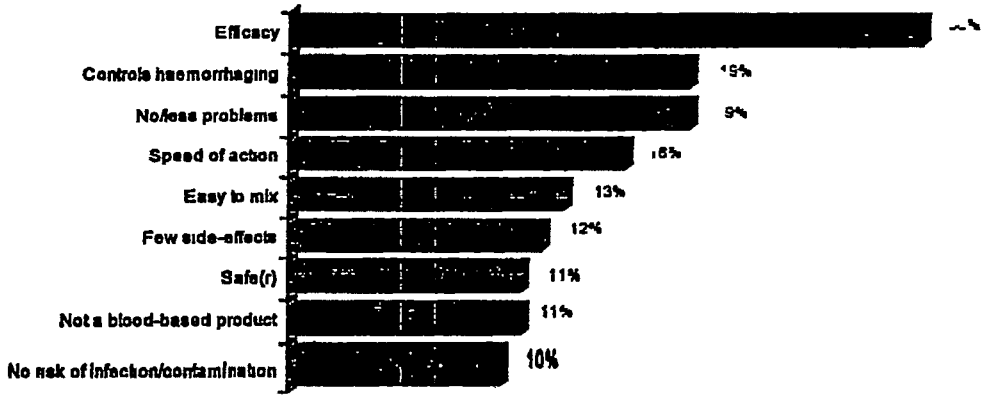


Base All respondents

The mean rating for both physicians and nurses was 4 1, with nurses in Sweden awarding the highest mean rating of 5 0 and nurses in Denmark awarding the lowest mean rating of 3 0 Among patients, the mean rating was 4 5 with the lowest mean rating of 3 8 being given by the patients in Spain There were five patients who claimed to be fairly dissatisfied with the currently available products (three in the UK, one in Spain and one in the USA), and five patients who claimed to be neither satisfied nor dissatisfied (three in Italy one in Spain and one in the USA)

Of those patients who were satisfied with the currently available rFVI products almost one third (30%) commented that this was due to the efficacy of the product. The chart below illustrates the most common reasons for patients satisfaction with the products currently available

Reasons for satisfaction with recombinant Factor VIII products



Base All patients who were satisfied with their rFVIII treatment (160)

3 10 Desired improvements

All respondents were asked to indicate which improvements they sought to the currently available rFVIII products, and those mentioned most often are listed in the following table

Desired improvement	Physicians (99)	Nurses (62)	Patients (172)
Reduced cost	67%	69%	34%
Reduced use of albumin/protein	56%	53%	36%
Longer lasting effect/half-life	46%	37%	43%
Improved supply/availability	45%	55%	3%
Reduced immunity/resistance/inhibitor development	44%	42%	0%
Reduced/no (viral) contamination	39%	39%	28%
Improved safety	28%	39%	24%
Improved storage (refrigeration not required)	27%	24%	32%
Easier administration	24%	23%	27%
Improved packaging/less wastage of ancillary products	14%	44%	18%

Interestingly, improved packaging/less wastage of ancillary products was mentioned by almost half of the nurses, making it the fourth most frequently mentioned improvement among this group, whereas this was a desired improvement for just 18% of patients and 14% of physicians

Improved storage ability was the fourth most important improvement for patients and was mentioned by almost one third of this group This improvement was also mentioned by almost one quarter of the physician and nurse groups

There were some interesting regional variations

- among patients in the USA, reduced cost was the improvement mentioned most often (45%),
- while reduced use of albumin/protein was mentioned by 56% of all physicians and 53% of all nurses, this improvement was mentioned by four out of five of the Japanese doctors but only one-fifth of nurses in Japan and the UK. For patients in Italy, this was the most important desired improvement
- longer lasting effect/longer half-life was the most commonly mentioned desired improvement among patients in France, Spain and Denmark. It was also commonly mentioned by physicians in the same countries
- improved supply/availability was less important for physicians in Spain and Japan (one in five) than for physicians in Sweden (four out of five
- improved storage (refrigeration not required) was perceived to be more important in Japan than in the other countries in this study
- reduced/no (viral) contamination was more important to physicians in Italy and France than in other countries

4 Relative importance of recombinant FVI I product features

4 1 Recombinant FVIII full profile conjoint task

In this study, a full profile conjoint task was undertaken during the interviews (see Appendix II for an explanation of the conjoint technique) The physicians and nurses were shown 32 cards and the patients 25 cards, each card describing a potential rFVIII product (see cards in Appendix I) Each card contained a different combination of attribute levels (different attributes were used for the different respondent groups according to their relevance to that group) The respondents were asked to rank the cards in order of preference

The attributes and their levels were as follows

1) *Human protein*
   - i) used in manufacturing and stabilising (final formulation)
   - ii) used in manufacturing (culturing), but not in the final formulation (for stabilising)
   - iii) not used at all

   This attribute was included in the tasks for doctors, nurses and patients

2) *Continuous infusion*
   - i) an approved indication
   - ii) product has capability, but not approved (label indication)
   - ii) not possible

   This attribute was included in the tasks for doctors and nurses only

3) *Diluent volume*
   - i) 2 5ml
   - i) 5ml
   - i i) 10ml

   This attribute was included in the tasks for doctors, nurses and patients

4) *High potency*

i) 1,000 i u

ii) 1,250 i u

iii) 1,500 i u

iv) 2,000 i u

This attribute was included in the tasks for doctors nurses and patients

5) *Assay issue*

i) requires one-stage assay

ii) requires chromogenic assay (not available in every hospital

This attribute was included in the tasks for doctors and nurses on

6) *Room temperature storage*

i) Cannot be stored at room temperature (requires refrigeration

ii) 3 months

iii) 6 months

iv) 1 year

v) 2+ years

This attribute was included in the tasks for doctors nurses and patients

7) *Reconstitution*

i) current standard (two vials)

ii) current standard, with needleless reconstitution/mixing

iii) single step procedure (i e pre-filled, ready-to-use syringe

This attribute was included in the tasks for nurses and patients on

8) *rFVIII molecule*

i) full length

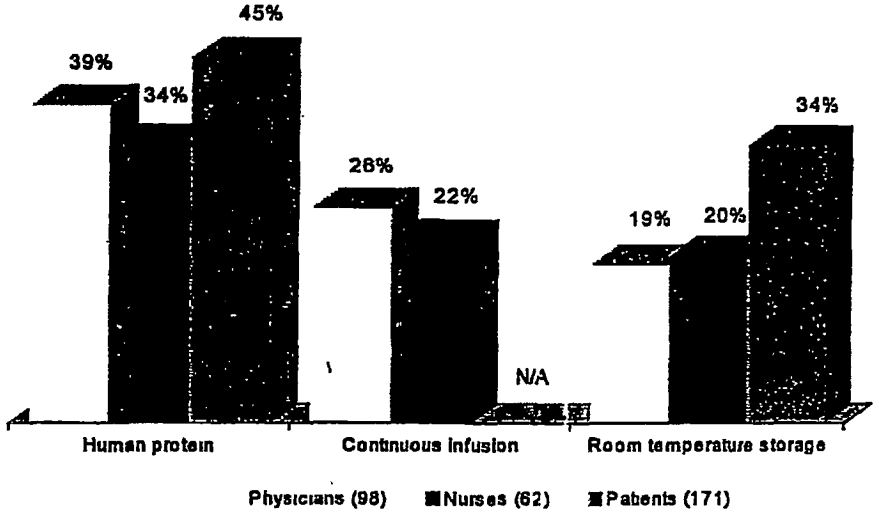
ii) B-domain deleted

This attribute was included in the tasks for doctors only

4 2 Relative importance of attributes and levels within attributes

The results of the conjoint analysis indicated that he human protein attribute was the most influential in the respondents' choice of product. This was the case for physicians, nurses and patients

Relative importance of most importan product features



Base All respondents

The following table shows the relative importance of each attribute in relation to the respondent's selection and ranking of the preferred products

	Physicians (98)	Nurses (62)	Patients (171)
1	Human protein 39%	Human protein 34%	Human protein 45%
2	Continuous infusion 26%	Continuous infusion 22%	Room temperature storage 34%
3	Room temperature storage 19%	Room temperature storage 20%	Reconstitution 14%
4	Assay issue 11%	Reconstitution 7% Diluent volume 7%	High potency 8%
5	High potency 3%		Diluent volume 3%
6	Diluent volume 1%	Assay issue 5%	
	rFVIII molecule 1%	High potency 5%	

The preferred levels within each attribute were also almost identical across the three groups of respondents

The following table illustrates the favoured product features (with the utility values for the preferred level) for each group of respondents

Physicians (98)	Nurses (62)	Patients (171)
Human protein not used at all (11 2)	Human protein not used at all (10 2)	Human protein not used at all (9 1)
Continuous infusion an approved indication (7 3)	Continuous infusion an approved indication (3 6)	*
Diluent volume 2 5ml (2 1)	Diluent volume 2 5ml (3 8)	Diluent volume 2 5ml (2 4)
High potency 1,500 i u (2 1)	High potency 2,000 u (2 8)	High potency 1,500 i u (3 1)
Requires one-stage assay (3 4)	Requires one-stage assay (2 4)	*
Room temperature storage 2+ years (6 2)	Room temperature storage 2+ years (7 7)	Room temperature storage 2+ years (7 6)
*	Reconstitution – single step procedure (i e pre-filled ready-to-use synnge) (2 9)	Reconstitution – single step procedure (i e pre-filled ready-to-use synnge) (3 4)
rFVIII molecule – Full length (1 1)	*	*

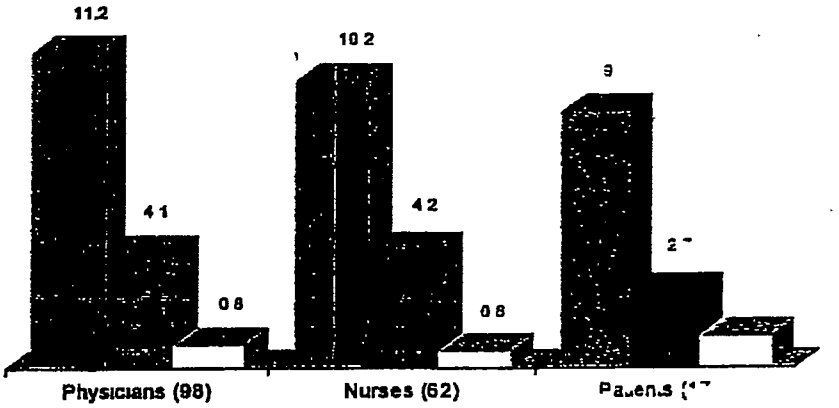
*These attributes were not included in the product features for this group of respondents

It is important to note the distance between the utility values of the levels for each attribute, as this is what dictates the attribute's importance - the greater the distance, the more important the attribute

4 2 1 *Human protein*

The greatest difference between the utility values for all three respondent groups occurred with the human protein attribute, making this attribute the most important to all groups in choosing a product The following chart illustrates the large degree of difference between the utility values, and thus the high level of importance placed on the human protein attribute

Utility values for human protein



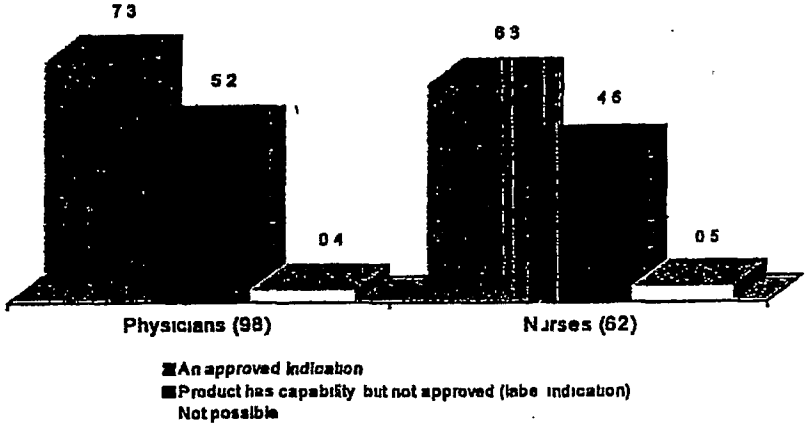
Base All respondents

The distance from the most popular attribute level to the second most popular is greater than the distance from the second most popular level to the least popular level This indicates that containing no human protein is of far more importance to the respondents than human protein being used at only one stage of production

4 2 2 *Continuous infusion*

The continuous infusion attribute was included ir the tasks for physicians and nurses only The total difference between the utility values for being approved for continuous infusion (the preferred level) to not being capable of use for continuous infusion (the least popular level), equated to 6 9 points for physicians and 6 1 points for nurses This was the second most importan attribute for these groups of respondents in selecting a product.

Utility values for continuous infusion being an approved indication



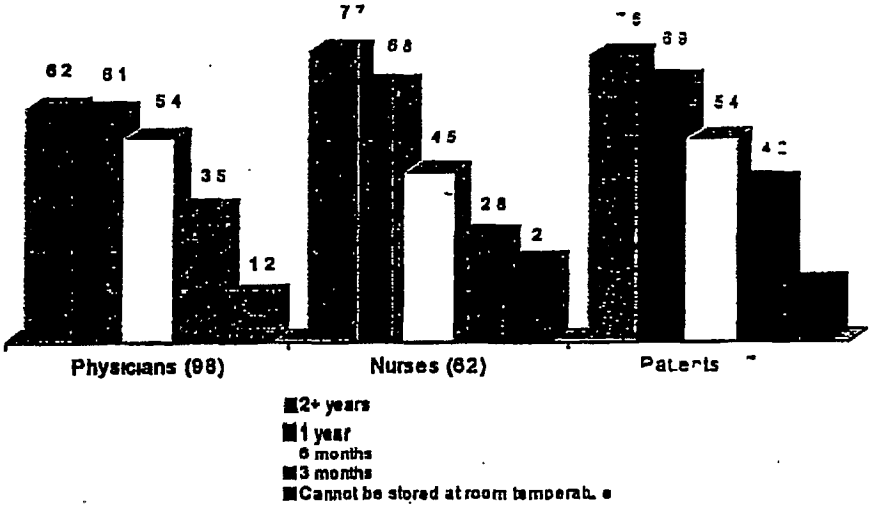
Base All physicians and nurses

There was a much larger difference between the second and third most popular levels than between the preferred and the second most popular levels This indicates that a potential rFVIII product being approved for continuous infusion is ideal, however one that has the capability (but is not approved for this indication) would also be considered important. The respondents were disinterested in a product that was not capable of being administered by continuous infusion

4 2 3 *Room temperature storage*

Room temperature storage was the second most important attribute for patients and the third for physicians and nurses The point differences from the most popular level (2+ years) to the least popular level (not possible to store at room temperature) were 5 0 points for physicians, 5 6 points for nurses and 6 points to patients

Utility values for room temperature storage



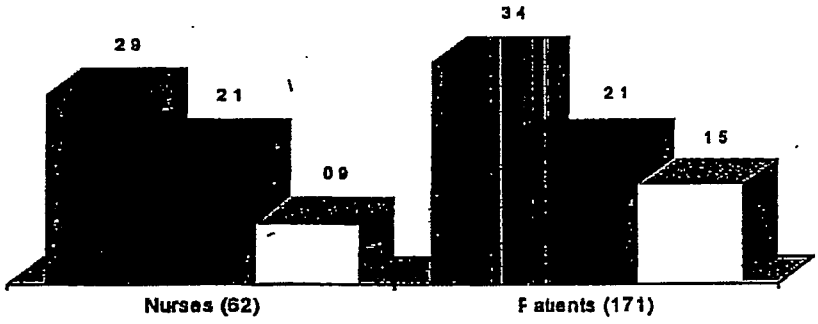
Base All respondents

It is interesting to note that the greatest difference between levels observed for physicians and patients from the inability to be stored at room temperature to three month room temperature storage, indicating that any storage time at room temperature was far preferable to requiring refrigeration

4 2 4 *Reconstitution*

The reconstitution attribute was included in the tasks for nurses and patients only It was the third most important attribute for patients and fourth equal for nurses The point differences between the least and most popular levels were 2 0 points for nurses and 1 9 points for patients The most popular level was single step procedure (pre-filled, ready-to-use syringe) and the least popular level was the current standard with two vials and transfer needles

Utility values for reconstitution



Base All nurses and patients

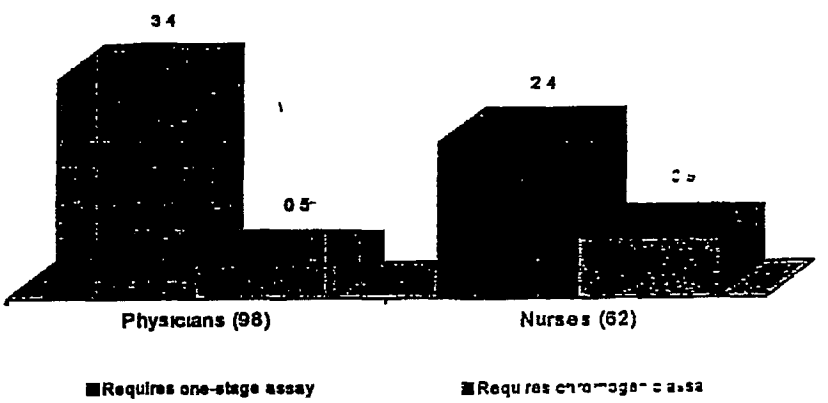
There was a greater difference for nurses between reconstituting using the current standard and reconstituting using the current standard without needles (1 2), than reconstituting with the current standard without needles and using a single step procedure (0 8) This would indicate that nurses would prefer to use a single-step procedure but there could also be an advantage in developing a product using the current reconstitution standard but without needles

In contrast, a needleless version of the current standard was not seen to be a significant improvement for patients, whereas a single step procedure would be

4 2 5 *Assay issue*

The assay issue was included in the tasks for physicians and nurses only and there was a difference of 2 9 points for physicians and 1 5 points for nurses from the more popular one-stage assay to the less popular chromogenic assa

Utility values for the assay issue

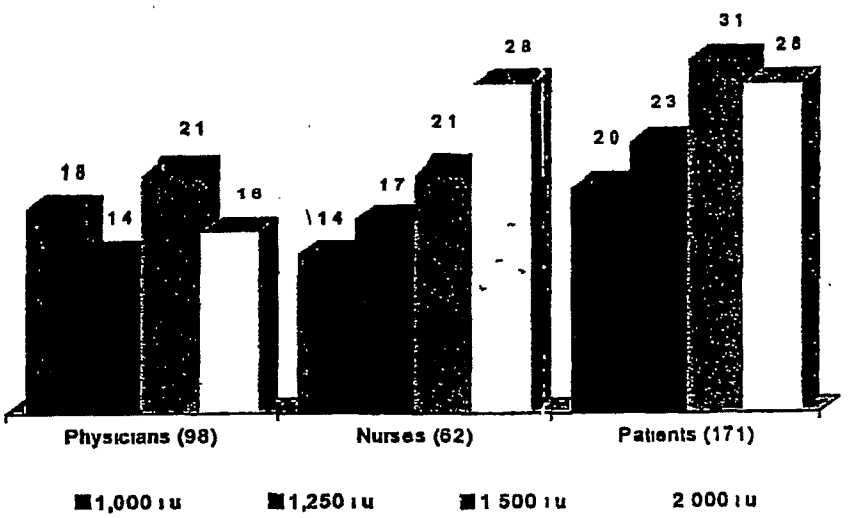


Base All physicians and nurses

4 2 6 *High potency*

The high potency attribute emerged with a low degree of influence on respondents, being the second least important attribute for patients, physicians and nurses There was a small 0 5 point difference between levels for physicians, a 1 4 point difference for nurses and a 1 1 point difference for patients The most popular choice was 2,000 i u for nurses and 1,500 i u for physicians and patients, the least popular potency was 1,250 i u for physicians and 1,000 i u for nurses and patients

Utility values for high potency

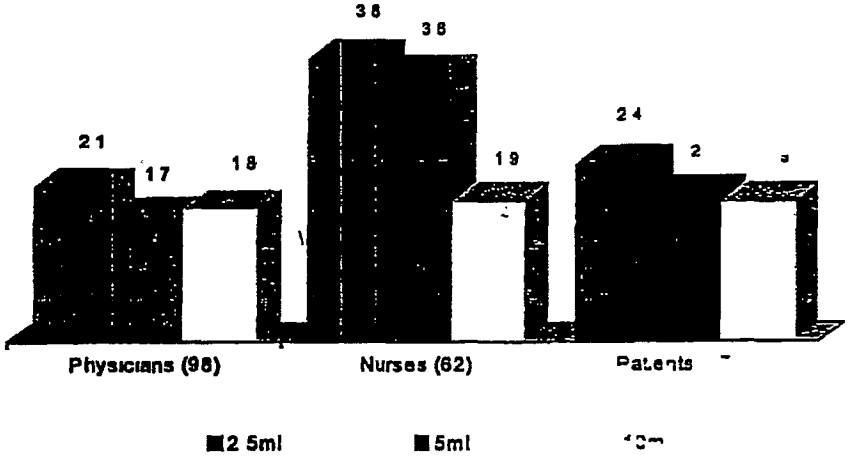


Base All respondents

4 2 7 Diluent volume

The diluent volume attribute was relatively unimportant in product selection scoring a 0 4 point difference for physicians, a 1 9 point difference for nurses and a 3 5 point difference for patients The most popular diluent volume was 2 5 ml for all groups of respondents and the least popular was 5ml for physicians and 10ml for nurses and patients

Utility values for diluent volume

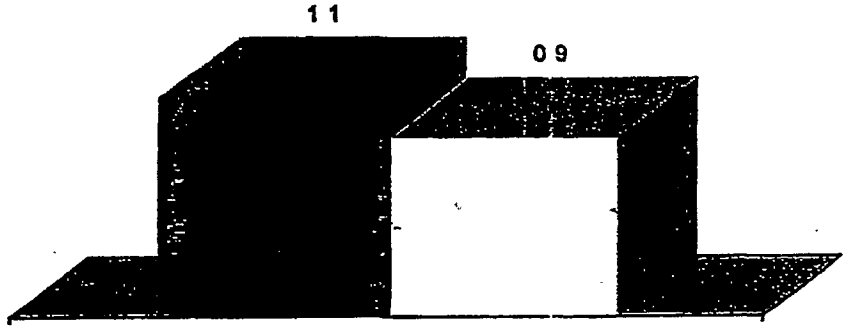


Base All respondents

4 2 8 *rFVIII molecule*

Physicians' tasks also included a preference for a full-length rFVIII molecule or a B-domain deleted molecule This was considered the least important attribute for the physicians, scoring a 0 2 point difference, with the full length molecule being minimally preferred (1 1 points) to the B-domain deleted rFVIII molecule (0 9 points)

Utility values for rFVIII molecule



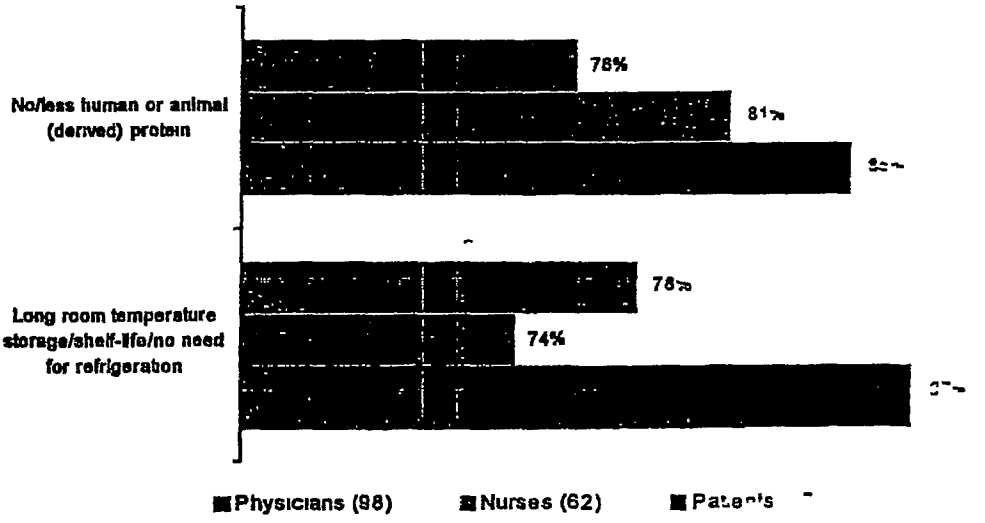
Base All physicians (98)

4 3 Reasons for ranking preferred product first

Respondents were asked to give their reasons for ranking their preferred product first The two most common reasons among all three respondent groups were

- no/less human or animal derived protein,
- long room temperature storage/shelf-life/no need for refrigeration

Reasons for ranking preferred product first

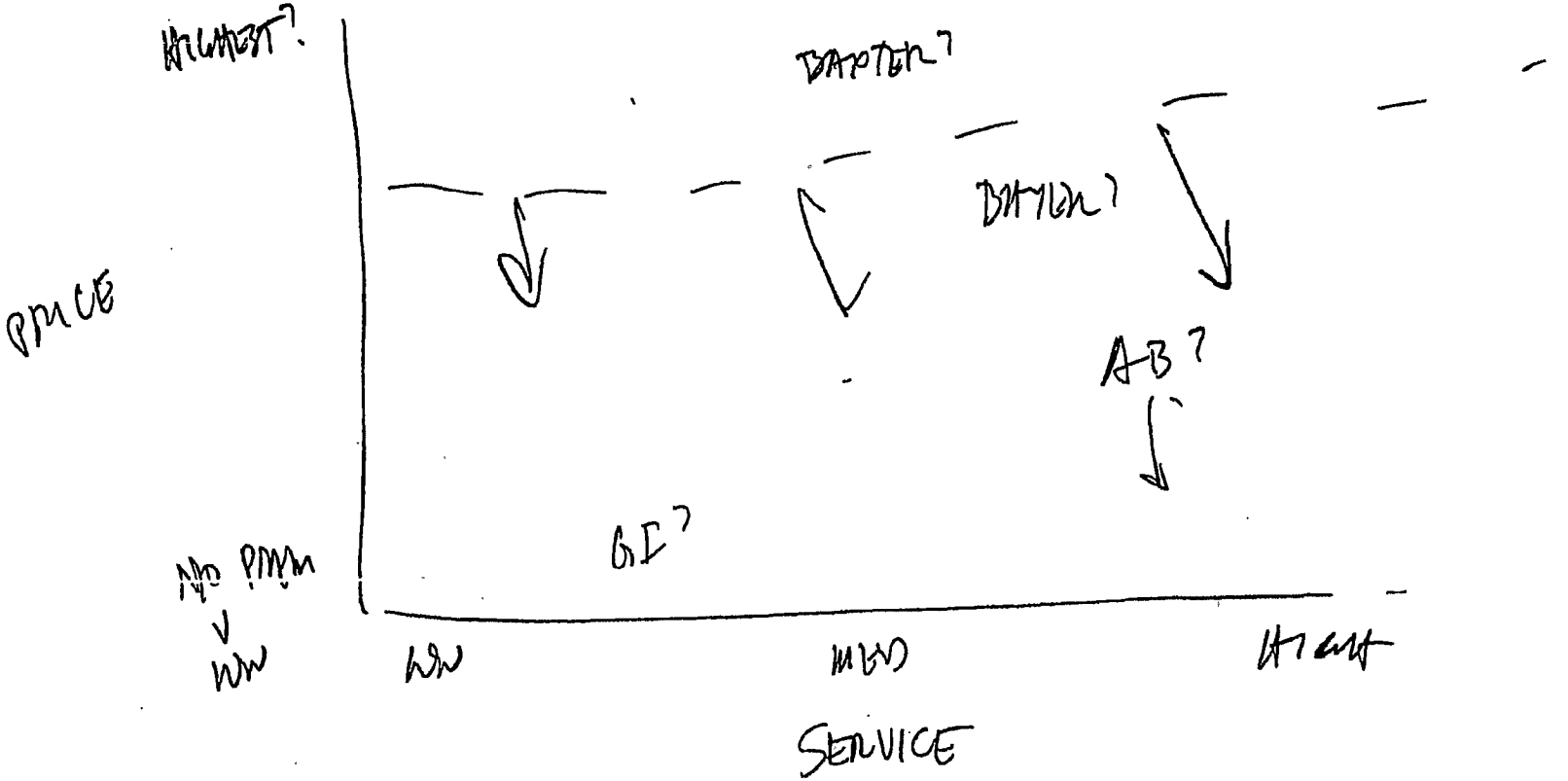


Base All physicians, nurses and patients

The third most common reason among physicians and nurses for selecting their chosen product, was that it was approved for continuous infusion

The pre-filled, ready-to-use syringe was the third most common reason for patients mentioned by more than half of this group, and it was the fourth most common reason for nurses This feature was only mentioned by two physicians

Customers: The level of the price premium will be a key factor in positioning our PFM brand

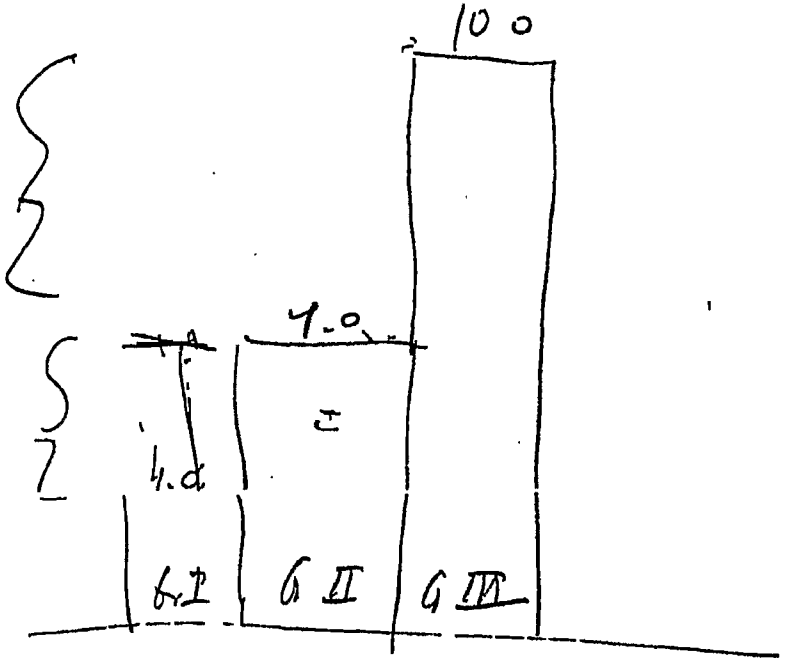


POTENTIAL PREMIUM

Customer: All things being equal, the customers will accept an XX% premium over Gen I products

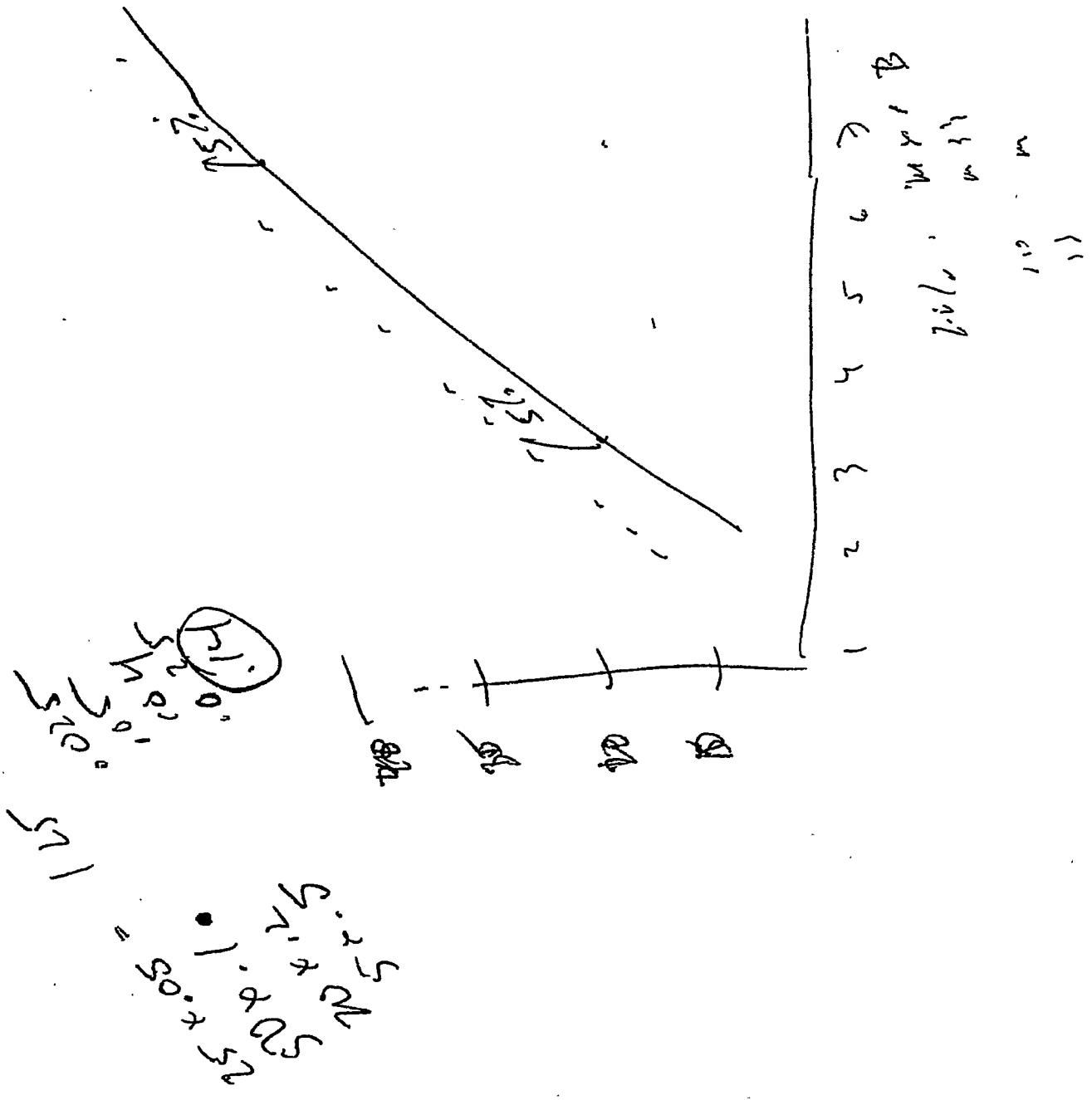
	premium based on utility Δ	premium based on market stated premium	premium based on actual premium
GII → GIII	6.0	10–20%	RANGE
GI → GII	3.0	20%*	(40%**)

UTILITY VALUES FOR HUMAN PROTEIN



* MANTEC
** PHI NOPHARMACIA
** MPB

Baxter

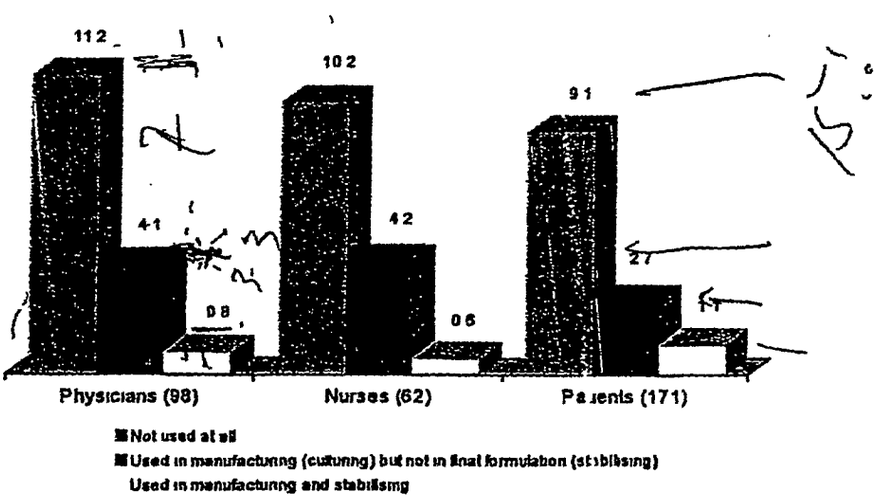


It is important to note the distance between the utility values of the levels within each attribute, as this is what dictates the attribu e's importance - the greater the distance, the more important the attribute

4 2 1 *Human protein*

The greatest difference between the utility values for all three respondent groups occurred with the human protein attribute, making th is attribute the most important to all groups in choosing a product The following ch art illustrates the large degree of difference between the utility values, and thus the high level of importance placed on the human protein attribute

Utility values for human protein



Base All respondents

The distance from the most popular attribute level to the second most popular is greater than the distance from the second most popular level to the least popular level This indicates that containing no human protein is of far more importance to the respondents than human protein being used at only one stage of production

Gen I > Gen II Pricing

	KG	KG-FS	% Premium	HLX	HLX-FS	% Premium	RECOMB	KG-FS 2000 % Prem vs Recom	HLX-FS % Prem vs Recom	REFACTO	REFACTO 2000 % Prem vs Recomb
NA	0 7500	1 130	51%	0 670	0 800	19%	0 719	57%	11%	0	0%
EU	0 557	0 630	13%	0 563	0 63	12%	0 566	11%	11%	0 565	0%

2000 > 2000 Pricing

	2000 KG-FS	2001 KG-FS	% Premium	2000 HLX-FS	2001 HLX-FS	% Premium	RECOMB	KG-FS 2001 % Prem vs Recom	HLX-FS % Prem vs Recom	REFACTO	REFACTO % Prem vs Recomb
NA	1 130	1 130	0%	0 800	0 800	0%	0 736	54%	9%	0 84	14%
EU	0 63	0 600	-5%	0 63	0 59	-6%	0 566	6%	4%	0 565	0%

4 4 Level of interest in using preferred product

Almost all of the physicians, nurses and patients in this study stated that they would be interested in using the product that they had ranked first. Only five patients (all from the USA) stated that they would not be particularly interested in using the product. Of those interested in using their selected product, approximately half said they would be willing to advocate paying a premium for the product (this was asked of physicians in all countries and of nurses and patients in the USA)

Of the 51 physicians, 18 nurses and 37 patients who indicated that they were willing to pay a price premium for their favoured product, more than half were willing to pay up to 10% Approximately another one fifth were prepared to pay up to 20% and a much smaller proportion were willing to pay up to 50%, the latter being mainly patients from the USA Six respondents stated that it would depend on their ability to pay for/afford the product and insurance coverage

J500398
EM/KW/MP/AB
12th June 2000

Appendix II

Trade-off/conjoint

(a) Attribute list
(b) Statistical results
(c) Background

500398 – Haemophilia

Attributes for conjoint

1 *Human protein*

i) used in manufacturing and stabilising (final formulation)

ii) used in manufacturing (culturing, but not in the final formulation (for stabilising)

iii) not used at all

2 *Continuous infusion*

i) an approved indication

ii) product has capability, but not approved (label indication)

iii) not possible (to be used for continuous infusion)

3 *Diluent volume*

i) 2.5ml

ii) 5ml

iii) 10ml

4 *High potency*

i) 1,000 i.u

ii) 1,250 i.u

iii) 1,500 i.u

iv) 2,000 i.u

5 *Assay issue*

i) requires one-stage assay

ii) requires chromogenic assay (not available in every hospital)

6 *Room temperature storage*

i) Cannot be stored at room emperature (requires refrigeration)

ii) 3 months

iii) 6 months

iv) 1 year

v) 2+ years

7 *Reconstitution*

i) current standard (two vials) with transfer needles

ii) current standard, with needleless reconstitution mixing

iii) single step procedure (i e pre-filled, ready-to-use syringe

8 rFVIII molecule

i) full length

ii) B-domain deleted

Doctors

1 Human protein

2 Continuous infusion

3 Diluent volume

4 High potency

5 Assay issue

6 Room temperature storage

8 rFVIII molecule

Nurses

1 Human protein

2 Continuous infusion

3 Diluent volume

4 High potency

5 Assay issue

6 Room temperature storage

7 Reconstitution

Patients

1 Human protein

3 Diluent volume

4 High potency

6 Room temperature storage

7 Reconstitution

J500398

Utility & Average Importances

Attributes	Doctors Mean	se	Nurses Mean	se	Patients Mean	se
1 Human protein	**39%**		**34%**		**45%**	
Used in manufacturing and stabilising (final formulation)	0 8	0 3	0 6	0 2	1 1	0 2
Used in manufacturing (culturing), but not in the final formulation (for stabilising)	4 1	0 4	4 2	0 5	2 7	0 3
Not used at all	11 2	0 6	10 2	0 8	9 1	0 4
2 Continuous infusion	**26%**		**22%**		**0%**	
An approved indication	7 3	0 5	6 6	0 7		
Product has capability, but not approved (label indication)	5 2	0 5	4 6	0 5		
Not possible (to be used for continuous infusion)	0 4	0 2	0 5	0 2		
3 Diluent volume	**1%**		**7%**		**3%**	
2 5ml	2 1	0 3	3 8	0 5	2 4	0 2
5ml	1 7	0 2	3 6	0 5	2 0	0 2
10ml	1 8	0 3	1 9	0 3	1 9	0 2
4 High potency	**3%**		**5%**		**6%**	
1,000 i u	1 8	0 2	1 4	0 3	2 0	0 2
1,250 i u	1 4	0 2	1 7	0 2	2 3	0 2
1,500 i u	2 1	0 2	2 1	0 3	3 1	0 2
2,000 i u	1 6	0 2	2 8	0 4	2 8	0 2
5 Assay issue	**11%**		**5%**		**0%**	
Requires one-stage assay	3 4	0 4	2 4	0 4		
Requires chromogenic assay (not available in every hospital)	0 5	0 1	0 9	0 2		
6 Room temperature storage	**19%**		**20%**		**34%**	
Cannot be stored a room temperature (requires refrigeration)	1 2	0 3	2 1	0 4	1 5	0 3
3 months	3 5	0 4	2 8	0 4	4 2	0 3
6 months	5 4	0 4	4 5	0 5	5 4	0 3
1 year	6 1	0 5	6 8	0 6	6 9	0 3
2+ years	6 2	0 5	7 7	0 7	7 6	0 4
7 Reconstitution	**0%**		**7%**		**11%**	
Current standard (two vials) with transfer needles			0 9	0 2	1 5	0 1
Current standard, with needleless reconstitution/mixing			2 1	0 3	2 1	0 2
Single step procedure (i e pre-filled, ready-to-use syringe)			2 9	0 5	3 4	0 2
8 rFVIII molecule	**1%**		**0%**		**0%**	
Full length	1 1	0 2				
B-domain deleted	0 9	0 2				
Base	98		62		171	

Trade-off / Conjoint analysis

1. Background

A common problem often encountered within the research arena is that of measuring the relative importance of attributes within a product Trade-off analysis decomposes the product into a number of features or attributes The respondents then trade-off these attributes against one another, forcing them to indicate their preferences From this information, it is possible to establish the relative importance of each of the attributes – thus providing a wealth of useful, clear information and powerful modelling capabilities

2. Full profile conjoint

2 1 Methodology

A full profile conjoint technique is one whereby

- each attribute is further broken down into different levels,
- product concepts are formed by combining different attribute levels,
- respondents are presented with cards each containing different product concepts,
- respondents are asked to rank the cards in order of preference

This forces respondents to trade-off all the attributes against one another at the same time

2 2 Analysis and utilities

The full profile conjoint technique produces rankings for attribute combinations Modelling techniques are then used to produce utilities for each level of each of the attributes The utilities are measures of the value or attractiveness of each attribute level to respondents They are calculated for each individual respondent A measure of importance is also derived for each attribute This shows how important the attribute is in the choice process These are produced for the whole respondent set

The utilities are used to

- identify the most popular options within an attribute – the higher the utility the more popular the option or level,
- measure the importance of the attributes - the distance between the most and least popular levels within an attribute dictate the attribute's importance
- assess the value of different product combinations - the utilities are additive

Having collected rankings on a small subset of all possible product concepts or combinations, we can calculate the relative preference for every possible product combination This is done by simply adding together the utilities of each of the attribute levels within a product concept

These product utilities can be calculated on an individual respondent basis They can then be compared – the product with the highest utility will be the one that the respondent will prefer Hence we can estimate market share for different products simulating the marketplace We can fine-tune products to maximise market share or minimise cost whilst maintaining market share

Re FV III

Intelligence Report

6/00

RECOMBINANT FACTOR VIII INTELLIGENCE REPORT JUNE 2000

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RECOMBINANT FACTOR VIII INTELLIGENCE REPORT

EXECUTIVE SUMMARY

This competitive intelligence research was begun in February 2000 to assess the competitive threat posed by Bayer's Kogenate SF® and Genetics Institute Refacto® The objective was to estimate as accurately as possible the launch dates for these products in key global markets and estimate the current and potential manufacturing capacity for these products

KEY FINDINGS

The key findings of this research are summarized in the table below

Product	Manufacturing Sites and Capacity	Date of Full Production	Launch Dates
Kogenate SF®	Berkeley, CA <1000 MAU Wuppertal, Gemany Unknown	3Q00 2005	EU July 2000 NA 2H00 Japan 2001 Australia 4Q00 NZ Launched
Refacto®	Stockholm,Sweden <250MAU St Louis, MO Unknown Dublin, Ireland Unknown	In production 2002 2004	EU Launched NA March 2000 (effective 4Q01) Japan Yamanuochi filing Australia No schedule NZ No schedule
Recombinate®	Thousand Oaks, CA 750-825MAU Neuchatel,Swit 750-1000MAU	4Q00 3Q02	EU 1Q03 NA 3Q02

Notes on table

- Bayer has not yet made a final decision on Wuppertal as the European manufacturing site
- GI was only able to sell approximately 100 MAUs of Refacto® in 1999, therefore the actual capacity for Stockholm is given as less than 250 MAU
- Due to supply issues, Refacto® is not expected to be a significant player in the North American market until 2002
- Baxter Neuchatel capacity will be 750 MAU for old formulation and 1000MAU for protein-free formulation
- Launch dates for Recombinate® are the projected approval dates for the protein-free formulation

RECOMBINANT FACTOR VIII INTELLIGENCE REPORT

Major Events Timeline

Item	3Q00	4Q00	1Q01	2Q01	3Q01	4Q01	2002	2003	2004	2005
Bayer Berkeley Site full production	•									
Bayer Wuppertal full production										•
GI St Louis in full production						•				
GI Dublin in full production									•	
Baxter TO in full production		•								
Baxter Neuchatel in full production								3Q03		
Kogenate SF® NA approval	2HOO	2HOO								
Kogenate SF® EU approval	July 2000									
Kogenate SF® Japan approval			•	•	•	•				
Kogenate SF® Australia approval		•								

PROJECT BACKGROUND

Since the mid-1990s, the manufacturers of rFVIII products have taken initiatives to both improve the safety and increase the available global inventory of these products The result has been the introduction of new products with reduced amounts of human proteins and thus reducing the chance of viral infection such as took place in the late 1980s and early 1990s

Beyond the introduction of new and safer products, the industry has seen a significant increase in the planned manufacturing capacity for rFVIII products

Baxter Hyland Immuno's key new competitors in the rFVIII market are Bayer Corporation's Kogenate SF® and Genetic Institute's Refacto® It is therefore critical that Baxter Hyland Immuno's senior management be aware of the details surrounding these two products' timing of launch in various regional markets and the near-term supply of these products

The ultimate concern by Baxter is that as the global manufacturing capacity of rFVIII suppliers increases significantly over the next five years, the supply of rFVIII will ultimately outstrip demand This would create a new market dynamic in which rFVIII suppliers would find themselves in a competitive environment much more challenging than currently

OBJECTIVES

It was decided that the following broad questio answered in regards to both Bayer Corporation and Genetics Insi

- Current and near-term (out to 2005) capa
- Launch dates for new products in the U Se, and Japan
- Marketing strategies (especially pricing strategies) for launch of these products
- Overall rFVIII strategies (i e replace cions with new products or add new products to rFVIII pi)

METHODOLOGY

Data Collection Richard Loomis conducted extensiction to gather all available public information on the rFVIII marsources include commercial and public databases, Internet and publish

Analysis Raw data was then analyzed by Mr Loomis of interest w followed up with primary (human source) research Fim human sc collection were then integrated with raw secondarnd analyze significance in terms of Baxter Hyland's intelligence ne

Report This report was then compiled utilizing second primary material as well as analysis conducted by Mr Loomis iration wit Hyland staff in marketing and operations Human sourcetew sumr attached as an addendum to this report Copies of the sary sourc used in preparing this report are available on request Ides of hur are concealed to protect these persons from potentialbarrassr preserve them for future use

Ethics Mr Loomis operates within strict intelligence collection guidelines to ensure that Baxter Hyland Immuno does not incur legal or public relations liabilities that might stem from the use unethical methods Mr Loomis' intelligence collection methods are in keeping with the guidelines of the Society of Competitive Intelligence Professionals (SCIP) and are in compliance with all federal and local statutes covering privacy and commercial proprietary information

BAYER CORPORATION-KOGENATE SF®

CURRENT AND FUTURE MANUFACTURING CAPACITY

United States

Berkeley, California

Currently Kogenate and Kogenate SF® are manufactured at one location Berkeley, California. In 1996, Bayer began construction of a new Kogenate manufacturing facility on the Berkeley campus This new facility, building 60, is a 100 000 square foot plant with two bioreactor suites of six 200-liter bioreactors each for a total of twelve bioreactors plus two spare 200-liter bioreactors (See Addendum A engineering drawings)

According to Baxter manufacturing personnel, the new technology being used by Bayer could yield up to ten times the capacity of an equivalent sized bioreactor at Baxter [1] This means that a single, 200-liter bioreactor at Berkeley could theoretically produce the same amount as a 2000-liter bioreactor This translates into a theoretical maximum capacity for building 60 of 1000 MAUs per year (250 MAU per 3 bioreactors x 4 = 1000 MAU total)

However, due to the lower yields of BHK cells (the source material for Kogenate SF®) versus CHO cells (the source material for Recombinate) the actual production capacity of Bayer's Berkeley facility is likely to be somewhat less than 1000 MAUs [2]

In 1996 a Baxter internal memo reported that a Baxter scientist named R. De Vreese calculated Bayer's annual Kogenate capacity at their old facility (building 5A) to be approximately 200 MAUs [3] In the same memo that Bayer R&D personnel indicated in a prepared statement to the U S Congress in 1995 that 'Bayer is investing several hundred million dollars at each of the multipurpose facilities (Clayton, NC and Berkeley, CA) to nearly double manufacturing capacity and support leading-edge

[1] Interview - BDS Program Manager, Baxter Hyland Immuno
[2] Interview - Director of Operations, Baxter Hyland Immuno
[3] Internal memo, Baxter Hyland Immuno, June 12, 1996

research and development activities" From this statement Baxter personnel at the time estimated that the Berkeley facility could have an annual capacity of 500 MAUs of Kogenate

From this information, a reasonable estimated potential capacity range for Bayer s Berkeley facility is between 500 and 750 MAUs per year This assumes that the difficulties involved in using BHK cells as a source material cause a 25% loss of efficiency in the bioreaction

According an investor relations manager at Bayer AG in Germany, the expansion suite in Berkeley was fully installed in February 2000 and is currently under validation[4] According to Baxter operations personnel, if Bayer has already run conformance lots of Kogenate SF® through the expansion suite the facility could be approved as early as July 2000[5]

Europe

Wuppertal, Germany

In April, 1999 Bayer Chairman Manfred Schneider said Bayer plans to build a second genetic engineering production site for its hemophilia medication Kogenate Schneider went on to state "Our plant in Wuppertal also has a good chance with regards to the choice of location"[6] An investor relations manager at Bayer AG in Germany confirmed that Wuppertal was high on Bayer's list for a European Kogenate Plant The investor relations manager went on to state that the reason that Wuppertal was high on the site list is that currently Bayer does some Kogenate process development and also has a pilot plant at that location[7]

It must be stressed that as of May 2000, Bayer has not yet decided on a site for a European Kogenate plant and is focused on getting the expansion suite in Berkeley up and operating

[4] Interview - Investor Relations Manager, Bayer AG
[5] Interview - VP Global Manufacturing, Baxter Hyland Immuno
[6] AFX News April 28, 1999 Also reported in Chemical Business Newsbase May 5, 1999
[7] Interview - Investor Relations Manager, Bayer AG

PRODUCT LAUNCH DATES

United States and Canada

Originally, Bayer had expected to launch Kogenate SF® in both the U S and Canada in late March 2000 [8] However, due to delays in gaining approval Bayer sources now indicate that the company expects to launch Kogenate SF® in North America sometime during 2H00 [9]

Europe

In March 2000 the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medical Products recommended that the EU approve Kogenate SF® At the same time, Bayer stated that it expects the therapy, to become available on European markets during the summer of 2000 According to Baxter sources in Europe, the usual lead-time between publication of a positive opinion and actual marketing authorization is 3 months This means that Kogenate SF®/Helixate SF® can be expected on the European market by the end of June 2000 at the latest [11]

Japan and Asia

According to Bayer Corp sources in the U S Kogenate SF® is expected to be approved in Japan sometime in 2001 [12] In the same conversation, the company indicated the expected launch approval date in Australia is 4Q00 Kogenate SFS was approved in New Zealand in 4Q99

[8] Interview - Director of Government Relations, NHF
[9] Interview - Corporation Communications Manager, Bayer Corp
[10] AFX European Focus, March 27, 2000
[11] Internal memo, Baxter Hyland Europe, March 28, 2000
[12] Interview – Director, Public Policy & Communications, Bayer Corp

PRICING STRATEGY

Bayer has positioned Kogenate SF® as a replacement fo Kogenate and pricing in Europe to date has been identical to the old product [13] [14] G ven this, plus the fact that Bayer sources have indicated that they intend to stop produ ction of Kogenate as soon as Kogenate SF® is approved in the U S , it is expected th at pricing in the U S and Canada will be in line with the old pricing [15]

[13] Internal memo, Baxter Hyland Immuno, October 6, 1999
[14] Interview – Senior Product Manager, Baxter Hyland Immuno
[15] Interview – Corporate Communications Manager, Bayer Corp

GENETICS INSTITUTE REFACTO®

CURRENT AND FUTURE MANUFACTURING CAPACITY

United States

St. Louis, MO

In August 1998, Genetics Institute purchased a biotech manufacturing facility in the town of Berkeley, Missouri near St Louis This is one of the oldest biotech manufacturing facilities in the U S , having been originally built in the early 1980s

Rumors that GI was having problems bringing this facility on-line have been widespread Delays could be due to equipment problems or simply difficulties in bringing the plant into compliance with current FDA guidelines Since the St Louis facility was originally built, the guidelines for biotech manufacturing such as the U S Pharmacopoeia (currently USP 24 – NF 19 effective January 2000) have been revised considerably The expense and effort required to upgrade an existing facility to these new standards can be extreme

Certainly given that Refacto® is already approved in the U S it can be assumed that GI had hoped to have an adequate supply of the product available for the North American market and be supplying that market through their U S partner

Also, the U S Refacto® approval included an indication for limited prophylactic administration of Refacto® Although physicians often administer rFVIII products prophylacticly for severe hemophilia on an off-label basis to go through the trouble to gain regulatory approval for such an indication hints that the manufacturer expected to have a considerable supply This is because

[16] Interview – Director of Operations, Baxter Hyland Immuno

prophylactic use of rFVIII requires a much greater supply than conventional use of the product [17]

In January 1999, an individual interviewing for a quality assurance position at the St Louis facility was told that the plant was scheduled to be in consistency manufacturing in either 4Q99 or 1Q00 [18] This information correlates with company statements that the St Louis plant is scheduled to be in full production and approved by the FDA sometime in late 2001 [19] Further confirmation of a late 2001 or 2002 production date comes from the National Hemophilia Foundation Their sources in the field indicate that delays in St Louis are expected to push full production out to 2002 [20] For this reason, NHF believes that Refacto® will not have an impact on the U S market for two years despite the FDA approval of the product in March 2000

Europe

Stockholm, Sweden

Currently, Refacto® is manufactured for Genetics Institute at the Pharmacia & Upjohn facility in Stockholm Sweden This plant is considered to have a maximum capacity of 250 MAUs However, in 1999 GI only sold approximately 100 MAUs of Refacto® in the EU Further hints of production problems in Stockholm were indicated during a February 2000 meeting between Baxter marketing managers and American Home Products' European marketing personnel During this meeting the AHP executives indicated frustration regarding supply issues surrounding both Benefix and Refacto® [21]

Dublin, Ireland

In early April 2000 American Home Products announced plans to invest approximately $685 million to expand its Wyeth Medica Ireland manufacturing operations by building a new biotechnology facility at The Grange Castle in South

[17] Interview – Technical Marketing Manager, Baxter Hyland Immuno
[18] Interview – Director of Operations, Baxter Hyland Immuno
[19] Interview – VP North American Corporate Communications, American Home Products
[20] Interview – Director of Government Relations, NHF

Dublin County, Ireland The products planned to be manufactured at the expanded Ireland facility include "Antihaemophilic Factor VIII for patients with Haemophilia A formulated in the absence of Human Serum Albumin"[22] In the same announcement AHP indicated that the company planned to begin construction on this site in the Fall of 2000 and be operational sometime in 2004 Contacts at Genetics Institute in the United States indicated that construction of the plant in Ireland would not impact the company's plans for St Louis[23] This source went on to state that the company intended that Stockholm would continue to supply Refacto® to the EU and US (in small quantities) until St Louis was operational St Louis would supply the North American market, and Ireland would supply Refacto® globally

PRODUCT LAUNCH DATES

United States and Canada

The U S FDA approved Refacto® in early March 2000[24] However due to supply problems and delays in getting their St Louis plant on-line, Refacto® is not expected to be a major player in the North American market until 2002 The company has indicated that small amounts of the product may be diverted from Europe in the 3Q00[25]

Europe

Refacto® was approved in the EU in 2Q99 Since this approval, Refacto® has been able to sell to between 6 and 7% of the EU market According to Baxter sources in Europe, much of this initial success can be traced to shortages of old formulation Kogenate® in Europe in 1999[26]

[21] Interview – Director of Coagulation Products, Europe, Baxter Hyland Immuno
[22] AHP press release, April 4, 2000
[23] Interview – VP North American Corporate Communications, American Home Products
[24] AHP Press release, March 7, 2000
[25] Interview – Director of Government Relations, NHF
[26] Interview – Senior Marketing Analyst, Global Marketing, BaxterHyland Immuno

Japan and Asia

According to an AHP source in the U S , the regulatory filing for Refacto® in Japan is being handled by Yamanouchi Pharmaceuticals[27] The source did not know the projected approval date for Japan The source did indicate that the company had no current schedule for gaining approval of Refacto® in Australia or New Zealand

PRICING STRATEGY

According to Baxter Hyland sources in Europe, Refacto® has been unable to gain any price premium over other rFVIII products in the regulated market across Europe[28]

[27] Interview – VP International Corporate Communications, American Home Products
[28] Baxter internal memo, March 2000

OTHER MARKETING STRATEGIES

Promotional Spending

In the past year, American Home Products has given considerable money to the NHF most of this going to a general research such as a $2 5 million research grant[29]

Overcoming Objections to Chromogenic Assays

Originally, physicians were instructed that to properly administer Refacto® a chromogenic assay would have to be used with the product This requirement of chromogenic assays with Refacto® could have proven to be a considerable hurdle to effectively marketing the product However, AHP has developed a new standard (reagent) to use with one-stage assays to get accurate equivalent results as in chromogenic assays[30] This standard is being made available to laboratories in Europe at no charge

[29] Interview – Senior Product Manager, Baxter Hyland Immuno
[30] Interview – Director of Coagulation Products, Europe, Baxter Hyland Immuno

CONCLUSIONS

THE IMMEDIATE THREAT

Despite Refacto® being approved in both the EU and the United States, supply issues in GI's existing manufacturing facility and delays in approval of the St Louis plant will stall its effective entry into the North American market until at least late 2001 The immediate threat will come from Kogenate SF® The Berkeley facility has the capability to switch over to Kogenate SF® production and may have as much as a 750 MAU or greater annual capacity in 2HOO

THE LONG-TERM DILEMMA

Currently, there are only three major manufacturing facilities for rFVIII products, Pharmacia & Upjohn's Stockholm plant, Bayer's Berkeley facility, and Baxter Hyland s Thousand Oaks plant By as soon as 2005 there will be six rFVIII manufacturing facilities worldwide (with the addition of St Louis, Dublin and Wuppertal) Although the exact capacities of these new plants are difficult to accurately estimate at this time, it is extremely probable that global production capacity of rFVIII will outstrip demand for the product during the next four-year period

This shift from a seller's market to a highly competitive market where suppliers must fight for market share will dramatically alter the market dynamic for all rFVIII manufacturers More emphasis will have to be placed on, and resources dedicated to, marketing communications, advertising, and product promotions for existing rFVIII products Additionally, more emphasis will need to be placed on R&D efforts to shorten the time to market of improved hemophilia therapies to stay ahead of the competition in this therapeutic area.

NEXT STEPS

The following actions are recommended to track competitive developments in the rFVIII market as the market dynamic shifts in the upcoming months and years (Outsource recommendations for each item are noted in Italics Note In the context of this report, a primary researcher is an individual experienced in conducting one-on-one intelligence interviews in person or over the telephone)

- **Conduct a detailed intelligence analysis of GI's proposed production facilities in Missouri and Ireland.** This may entail visits to county level planning departments to review architectural and engineering drawings of these facilities In the case of Ireland, since construction is not scheduled to begin until fall 2000 the earliest that any engineering drawings are likely to be available and useful would be 4Q00 *(Recommendation Outsource to primary researcher familiar with this type of competitive intelligence work)*
- **Continue to track FDA approval of Bayer's Kogenate SF® expansion facility in Berkeley.** *(Recommendation Outsource to primary researcher)*
- **Monitor Bayer's final decision on a production facility in Europe** *(Recommendation Baxter monitor secondary sources outsource primary research on this item)*
- **Track historical, current, and planned advertising budgets for both Refacto® and Kogenate SF®** Look for dramatic increases in advertising budgets for both products In the case of Refacto®, this is not likely until mid-2001 *(Recommendation Outsource to advertising tracking service if possible and to primary researcher)*
- **Track print advertising for both Refacto® and Kogenate SF®** Utilize clipping services to view advertisements to analyze positioning and message Track frequency to estimate actual advertising spending *(Recommendation Outsource to clipping or advertising tracking service)*

- **Systematically contact Baxter marketing and sales personnel worldwide for intelligence collection including promotional materials from the field on competitive products.** *(Recommendation Baxter if resources are available, otherwise outsource to primary researcher to conduct scheduled debriefs with key marketing and sales personnel in the field)*
- **Continue contacts with key industry analysts and NHF contacts for shifts in supply issues in various markets** *(Recommendation Outsource to primary researcher)*
- **Track U.S., European and World patents relevant to current and future formulations of rFVIII products.** *(Recommendation Baxter if resources are available)*
- **Track pre-clinical and clinical trials of existing rFVIII formulations as well as future formulations** *(Recommendation Outsource to primary researcher)*

ADDENDA

Addendum C rFVIII Capacity and Market Projections to 2005

Year	Location	Capacity in MAU	Difference	Demand	
2000	Bayer Berkeley	850			Source P Marshall, Baxter
	GI Stockholm	250			Source H-P Halbritter, Baxter
	Baxter TO	825			Source R Murawski, Baxter
	Total	1,925	(75)	2,000	

Year	Location	Capacity in MAU			
2002	Bayer Berkeley	850			Source P Marshall, Baxter
	GI Stockholm	250			Source H-P Halbritter, Baxter
	GI St Louis	750			Estimate based on 100K sq ft
	Baxter TO	825			Source R Murawski, Baxter
	Total	2,675	(25)	2,700	

Year	Location	Capacity in MAU			
2003	Bayer Berkeley	850			Source P Marshall, Baxter
	GI Stockholm	250			Source H-P Halbritter, Baxter
	GI St Louis	750			Estimate based on 100K sq ft
	Baxter TO	825			Source R Murawski, Baxter
	Baxter Neuchatel	900			Source R Murawski, Baxter
	Total	3,575	375	3,200	

Year	Location	Capacity in MAU			
2004	Bayer Berkeley	850			Source P Marshall, Baxter
	GI Stockholm	250			Source H-P Halbritter, Baxter
	GI St Louis	750			Estimate based on 100K sq ft
	GI Dublin	1,000			Estimate based on new plants
	Baxter TO	825			Source R Murawski, Baxter
	Baxter Neuchatel	900			Source R Murawski, Baxter
	Total	4,575	1,075	3,500	

Year	Location	Capacity in MAU			
2005	Bayer Berkeley	850			Source P Marshall, Baxter
	Bayer Europe	1,000			Estimate based on new plants
	GI Stockholm	250			Source H-P Halbritter, Baxter
	GI St Louis	750			Estimate based on 100K sq ft
	GI Dublin	1,000			Estimate based on new plants
	Baxter TO	825			Source R Murawski, Baxter
	Baxter Neuchatel	900			Source R Murawski, Baxter
	Total	5,575	2,075	3,500	

Notes

- Bayer Berkeley highest theoretical capacity is 1000MAU Capacity estimates were based on a review of equipment layout drawings of the plant and interviews with individuals involved with process development for Kogenate SF
- Bayer Europe manufacturing site has not yet been selected as of May 2000
- GI Stockholm has historically been producing less than 250MAU (100MAUs Refacto in 1999)
- Baxter Thousand Oaks capacity was actually given as a range from 750-825 MAUs
- Baxter Neuchatel capacity was actually given as a range from 750-1000 MAUs

COMPETITIVE SCOPE OF WORK: RESEARCH & KEY INTELLIGENCE TOPICS

NORTH AMERICA, CANADA, EUROPE, AND JAPAN

Genetics Institute Refacto® and protein free manufactured (PFM) Refacto

CAPACITY

- Confirm 250 MAU capacity at Stockholm plant

➢ Confirmed based on new plants coming on line in St Louis and Ireland

➢ Sold less than 100MAU in Europe in 1999

- Determine the usage and status of the St Louis plant will it be used for Refacto and/or for their PFM product

➢ St Louis plant will supply U S market and according to GI sources, is currently in validation and scheduled to be approved by the FDA and fully operational by late 2001

- Any other locations they want to start manufacturing

➢ AHP has announced plans to build biotech plant in County Dublin, Ireland According to GI sources in the U S , this plant will supply Refacto globally and is scheduled to be operational by sometime in 2004

- Ability to expand the Sweden and St Louis plant

➢ Ability to expand Sweden appears to be limited given expansion plans in St Louis and Ireland, as well as supply problems experienced in 1999 and early 2000 in Europe

- Time to ramp-up to full production Additional suites planned

➢ According to GI sources interviewed, St Louis is to be fully operational by late 2001 As a result, NHF does not expect Refacto to be a significant player in the U S FVIII market until 2002

- What is their worldwide supply/capacity potential?

➢ The capacity potential will remain 250 MAUs until at least late 2001 or early 2002

Addendum D

- Any changes in the purification train from Refacto to protein-free manufacture Refacto

➢ Still investigating this question

PRODUCT

- What is the precise launch date in the U S , Canada, Europe and Japan

➢ Expect small quantities of Refacto to enter U S distribution in September 2001 However, Refacto is not expected to be a significant player in U S until 2002

➢ AHP VP of International Communications indicates that Refacto® regulatory filing being handled by Yamanouchi Pharmaceuticals He was unaware of their timing of the filing The same source indicated that there are no immediate plans for seeking approval of Refacto® in Australia or New Zealand

- Any particular strategies for the launch

➢ GI will supply new assay standards at no cost to overcome objections regarding chronogenic assay issue

➢ Advertising promotional strategies are still being investigated

- Will they stop producing Refacto when they start PFM

➢ Still investigating

- What will be their pricing strategy?

➢ Pricing expected to be comparable to other existing rFVIII products

- Estimation of concurrent strategies for product launch (e g delivery systems protein modification, storage modifications, etc)

➢ None noted

- Clinical trial strategy (e g new license vs modification to current license)

- Any other products they are working on the pipeline

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ate SF®[®] and protein free manufactured (PFM) Kogenate

- ur at Berkley plant is only location for production

ur tly, yes manufacturing takes place at buildings 60 in Berkeley

- ny other ocations they want to start manufacturing

➢ According to sources interviewed at Bayer AG in Germany, Bayer is planning on building a Kogenate SF® plant in Europe A site has not been selected yet, however, Wuppertal Germany is high on the list

- Time to ramp-up to full production? Additional suites planned

➢ Full production could begin as soon as July 2000 at the expar sion suite in Berkeley

- What is the worldwide supply/capacity potential?

➢ Still pursuing this with Thousand Oaks We have detailed pl nt information for building 60 as well as fairly detailed information regarding b ilding 5A

➢ Assuming technology advances made in the new process gleaned from conversations with individuals involved in process development for Kogenate SF®®, the Berkeley facility will have a theoretical maximum capacity of 1000MA U However, due to difficulties inherent in the raw material used (BHK cells), the plant is expected to have a capacity somewhat less than this, approximately 850M AU

- Any changes in the purification train from Kogenate SF® to PFM Kogenate

➢ Still investigating this question

PRODUCT

- What is the precise launch date in the U S , Canada, Europe, and Japan

➢ Original launch date in the U S and Canada was late March 200, company sources now expect U S approval in 2H00, Japan approval sometime in 2001, and Australian approval in 4Q00 Kogenate SF® was approved in New Zealand in 4Q99

➢ Expected European launch date will be late June 2000

Addendum D

- Any particular strategies for the launch

- Will they stop producing Kogenate SF® when they start PFM?

  ➢ Unknown yet, however, given the strategy for Kogenate SF®, expect that Bayer would replace Kogenate SF® with PFM

- What will be their pricing strategy?

  ➢ If Europe is any indication, Kogenate SF® in North America will be priced similar to old formulation Kogenate®

- Estimation of concurrent strategies for product launch (e g delivery systems presen modification, storage modifications, etc)

  ➢ None found yet

- Clinical trial strategy (e g new license vs modification to current license)

- Any other products they are working on. the pipeline

ndex of Interviews

Vice President, Global Manufacturing, Biotech, Baxter Hyland Div.

Interview: BHI-01

Title: Vice President, Global Manufacturing, Biotech

Organization: Baxter Hyland Division

Background.

This source has worked in biotechnology manufacturing for 13 years and has been instrumental in the establishment of Baxter Hyland's production facility in Thousand Oaks California. The source has also worked as a manufacturing consultant to various biotech manufacturers, including Genetics Institute

Source Comments:

The source began the conversation by giving some background on the functions performed at the Baxter Hyland plant in Thousand Oaks This was to provide the analyst with a baseline of information regarding typical functions to be found in a biotech plant involved in Factor VIII production The Thousand Oaks facility performs cell culture, purification and fill finish for Recombinate Functional departments at Thousand Oaks included Validation, Quality Assurance, Human Resources, Maintenance, and Engineering

Currently, Baxter Hyland is operating a single suite of three stirred-tank bioreactors and is in the process of expanding to a total of three suites of nine bioreactors The bioreactors grow CHO cells to express Factor VIII

The source indicated that for this type of biotechnology production work manufacturers generally seek individuals with cell culture and biochemistry and or molecular biology backgrounds Typically, floor supervisors have B S or M S degrees, a purification supervisor may have a Ph D, and technicians generally have B S degrees

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·logy manufacturing ıs much more a mixture of craft and
ea .d pharmaceutical production This ıs due to the nature
· ,ures constant adjustment and "weakıng" to maxımize
.J 0 ıty

. th conversation to explaın some backgrou d on how bıotech fırms
.J, ıost all bıotech fırms begın as research and development organızatıons
· bıotechnology dıscovery and ıts clınıcal vıab.Lty After thıs phase ıs
.d close to completed, the emphasıs ıs then placed on process development
part of the preparatıon to go to market wıth a product, he fırm begıns to shıft ıts
·hr ogy emphasıs to full-scale commercıal manufacturıng

ıe source noted that many bıotech fırms faıl to make the transitıc n to full-scale productıon for a varıety cf reasons Thıs can ınclude problems ın scalıng .o a complex laboratory process to economical full-scale productıon There ıs also the possıbılıty that as the functıons expand from dıscovery to manufacturıng, less talente.d ındıvıduals are gıven responsıbılıty for developıng the manufacturıng capabılıty (In other words, the best mınds are focused on dıscovery, the second best mınds are responsıble for process development, and the thırd best mınds are gıven responsıbılıty for scalıng u.o productıon) Another possıble source of delay or even faılure of a bıotech fırm to reach the manufacturıng stage can be the ınvo'vement of thırd partıes such as contract manufacture rs or consultants These are just some of the reasons, accordıng to the source, that ıt can take years for a bıotech fırm to go from posıtıve clınıcal results to full-scale productıon and marketıng of bıotech product

The analyst asked the source about valıdatıon and ıts role ın the scal ng up of bıotech facılıty The source exp'aıned that valıdatıon of a bıotech productıon facılıty has two basıc purposes, one ıs to ınsure the consıstency, efficıency, and quality of the manu acturıng process, and the second purpose ıs to satısfy FDA regulatory requırements fo the documentatıon of procedures of a bıotechnology manufacturıng facılıty The source went on to explaın that valıdatıon ıs typıcally done annually or semı-annually At Baxter Hyland an ınternal department per'orms valıdatıon Some manufacturers retaın the servıces of thırd party valıdatıon companıes for thıs functıon

The analyst then asked the source if he had any specific knowledge of issues at manufacturing sites for Kogenate SF or Refacto The source indicated that he had knowledge of the Genetics Institute facility in St Louis prior to GI s takeover of that The source categorized the St Louis plant as "over-designed" The source had also rumors that GI was having trouble with their [Water for Injection-WFI] water supply Louis Regarding Bayer, the source had heard rumors that they were having trouble gro [BHK] cells Finally, the source had heard of high turnover in manufacturing personn Bayer

The source volunteered that when researching equipment manufacturers for Bayer it would be best to focus on German equipment manufacturers as "The Germans prefer to use German equipment, which also happens to be very good quality equipment

The analyst then asked the source to summarize some good base line measurements to use as we investigate capacity at the various competitors The source stated that most plants start with a production capacity goal, say for example, 250 MAUs per year The next step is to establish what the average yield is of the process involved In the case of Factor VIII a good ballpark figure would be 1 5g/L Next comes the number and size of the bioreactors Next comes the rate or time it takes for a typical cycle of a bioreactor In the case of Factor VIII a typical cycle takes 48 hours In a typical year, it can be expected that a production suite can run from 42-48 weeks with the remaining time absorbed by preventive maintenance Finally, a good average square footage required for a single three reactor suite would be 10,000 square feet

Armed with this information we can extrapolate annual production figures for a typical Factor VIII plant

Assumptions

90,000 square foot facility = 9 production suites

If each suite has a 10,000L working volume, each suite has a production per cycle (assuming a 1 5g/L yield) = 15,000g

If each cycle takes 48 hours, then all nine suites can produce 135,000g of Factor VIII in 48 hours If the plant runs on a continuous basis this would equate to 472 500g per week or 19,845,000g per year with 42 weeks of production

An important consideration in such calculations is whether a production facility is multi-product and then, if the bioreactors are run concurrently or in campaigns Information on this may be gathered from engineering firms involved in setting up the facility The engineering firm that is working on the expanded suites at Baxter also set up suites for Bayer in Berkeley

The analyst then asked the source to indicate some sources of information that could prove valuable when calculating a plant's capacity or relative time in scaling up production The source indicated that finding out how much and when a manufacturer ordered purification resin would be valuable There are very few suppliers of such resin and a major one is Pharmacia. Another material worth noting is Mab [monoclonal antibody] resin The key supplier in this case is Lonza (formerly Celltech) These resins are very expensive (costing millions of dollars) and are used in large quantities during the launch phase Another raw material used in Factor VIII production is BSA [Bovine Serum]

On the equipment side, the source indicated that there are few manufacturers of lyophilizers [freeze dryers used in preparation of final product] In the U S , Hull is a key manufacturer of lyophilizers

Related to equipment are any details regarding either industrial or human waste treatment facilities required of the manufacturing facility Many municipal ties require very detailed descriptions of waste treatment plants associated with biotech plants due to public health concerns If the capacity of a production facility's waste treatment plant is known, an estimate can be made of the planned production capacity for the facility

The number of people employed at the facility can also provide a clue as to the capacity of the facility

Water for Injection (WFI) stills and storage tanks are very important pieces of equipment in a production facility A single WFI storage tank typically holds one day s supply of water for the plant with many plants having a backup storage tank in reserve

Square footage of a plant is valuable information as mentioned earlier A 30 000-sq ft plant would be considered a pilot plant, with most full-scale production plants being more in the neighborhood of 150,000 sq ft

The capacity of any utilities of the plant (boilers, generators, etc) can also help in calculating an estimated production capacity for a facility Even the number and size of cooling towers at the plant can prove useful

Knowing whether a plant is automated or semi-automated can also be useful information

How many shifts and days per week of operation are also important

The type of bioreactors used at the plant can provide a clue to production capacity Many plants utilize stirred-tank bioreactors, but more recently, companies have begun using perfusion type reactors The source speculated that the newer facilities at Bayer and the CI plant in St Louis would use this type of reactor Smaller biotech firms may still have some hollow fiber type bioreactors because they still have this equipment from before they went to full-scale production

The conversation then shifted to specific information or rumor the source had heard regarding GI's plant in St Louis The source indicated that he had spoken with an individual who had interviewed for a quality assurance position at the St Louis plant. During the course of the interview process, the candidate was told that GI had two 600L perfusion reactors at St Louis in the fourth quarter of 1999

The interview then concluded and the source introduced the analyst to Baxter H. and s Director of Operations

Analyst Comments·

This source is an invaluable source of technical information and will be used throughout the project to clarify issues and assist in analysis of information collected

The rumor of Bayer having difficulties in growing cells may be related to their dependence upon BHK cells as a raw material These cells are notoriously unstable and difficult to work with (see comments in following interview)

The indications of high turnover in manufacturing personnel at Bayer mirrors anecdotal information on Bayer's sales force turnover collected recently from Baxter sales personnel

Director of Operations, Baxter Hyland Division

Interview: BHI-02

Title: Director of Operations

Organization: Baxter Hyland Division

Background:

This source is the plant manager for Baxter's Thousand Oaks facility and has considerable contacts within the biotech industry

The source could only speak briefly with the analyst but agreed to be a source for follow-up interviews as the project progressed

The source indicated that he had recently heard through contacts that considerable information is available on the Internet involving the details of the pending launch of Refacto The source agreed to go back to his source to discover where on the web this information was available

When asked about rumors of Bayer having problems growing cells the source stated that BHK cells are very unstable and difficult to work with The source further noted that other more stable cell mediums are currently used, however, Bayer may be stuck with BHK because the original regulatory approvals for Kogenate used this technology

It was the source's opinion that GI's St Louis plant is intended for Refacto production in North America and that Stockholm would supply the European markets The source characterized the St Louis plant as "antiquated" and having been up for sale for a considerable time

At this point the source had to leave to rejoin Canadian regulatory authorities visiting the plant that day

Analyst Comments:

Both this source and source BHI-01 had considerable knowledge of the St Louis plant before GI purchased it

This source has considerable manufacturing contacts within the biotech industry and will prove useful as a source of contact names as well as technical assistance in analysis of information and data collected for the project

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Investor Relations Manager, Baxter AG, Germany

Interview: BHI-03

Title: Investor Relations Manager

Organization Bayer AG

Background:

This source has direct access to information regarding strategic initiatives by all divisions of Bayer AG, including Bayer Corp in the U S

Source Comments:

The analyst approached the source as following up to comments made by Bayer Chairman, Manfred Schneider in April 1999 that Bayer was planning on building a second Kogenate SF® plant, possibly in Wuppertal, Germany

The source stated that the most recent capacity increase for Kogenate SF® production was at the Berkeley facility This was completed last month (February 2000) increasing fermenter size and output The change to the new process which unlike many competitors, is continuous and is currently in validation

The new suite at Berkeley will double the plant capacity (The source would not state how much this capacity would be or how long it would be before the plant reaches this capacity)

Regarding the building of new Kogenate SF® plant The source indicated that Bayer is planning to further increase Kogenate SF® capacity by building a second plant in Europe A number of sites for this plant are under consideration including Wuppertal Germany

The reason Wuppertal is being considered is that Bayer currently produces active ingredients for its pharmaceuticals at Wuppertal Also, Bayer conducts some Kogenate SF® process development at Wuppertal and has a Kogenate SF® pilot plant at that location

The source volunteered that Bayer decided to manufacture biotech products in the U S back in the mid-eighties when the political climate in Germany was problematic for biotech firms The source gave the example of Hoechst taking four or five years to gain approval for a biotech facility during this period The source indicated that the political climate in Germany has improved considerably so that the company feels comfortable planning biotech manufacturing in Germany

Analyst Comments:

This is the first confirmation that Bayer is planning to build a second Kogenate SF® plant This source was cooperative, but somewhat cautious asking the analyst's name and e-mail address

Director of Government Relations, National Hemophilia Foundation

Interview: BHI-04

Title. Director of Government Relations

Organization: National Hemophilia Foundation

Background:

This source oversees the preparation of NHF's Medical Advisories related to the supply of Factor VIII products The source has regular contact with Factor VIII manufacturers and is kept informed regarding supply issues of these products

The source confirmed that the last information NHF had on Kogenate SF® was that the late March 2000 launch of the product in the U S and Canada had been delayed into the 2Q00 However, the source is scheduled to meet with Bayer at the end of March 2000 to get a revised update on the Kogenate SF® launch

The analyst then mentioned rumors of problems that Genetics Institute was having at their St Louis plant with their water supply The source stated that he was unaware of these rumors, however, information he had from the field indicated that GI's St Louis plant would not be operational for another two years According to the source, beginning in 3Q00, AHP intends to divert small amounts of Refacto® from the European market to the U S These amounts will be so small though that "Refacto® being approved in the U S will not have an impact on the U S market for two years " The analyst asked the source if he had asked GI to confirm the two-year delay The source stated that he had brought this up with GI and that the company did not deny it

The conversation then shifted to gene therapies for hemophilia The source stated that Avigen had a Phase II clinical trial underway at Children's Hospital in Philadelphia This trial is for intramuscular administration of Factor IX using Adeno associated virus (AAV) as a vector The principal investigator for this trial is Kathy High

Avigen also submitted a Phase I protocol on March 9, 2000 at the meeting of the Recombinant DNA Advisory Committee of the FDA This clinical trial w[illegible] e Factor IX being administered directly to the liver without a vector The tria[illegible] ake place at Stanford University Medical Center in Palo Alto, California The principa investigator is Mark Kaye

The source also mentioned that Chiron has a Factor IX gene therapy Phase II tria underway at the University of Pittsburgh Medical Center

Finally, the source indicated that Transkaryotic Therapies has a Factor IX gene therap Phase I trial underway at Beth Israel Hospital in Boston

Analyst Comments:

This source was very cooperative and is in frequent contact with the larger organizations It is highly recommended that follow-up interviews be conducted with him after his next meetings with competitors and on a regular basis

Securities Analyst, Paine Webber

Interview. BHI-05

Title Securities Analyst

Organization Paine Webber Securities, New York

Background

This source is a senior biotech analyst at Paine Webber and a covering analyst for AHP The source has indirect information regarding strategic initiatives of AHP and GI This individual is a frequently contacted source by the analyst and exchanges information on a monthly basis with the analyst on a number of biotech and pharmaceutical companies

Source Comments

The source confirmed that the original launch date of Kogenate SF in the U S and Canada was late March 2000 and that the current delay of launch is due to the delay in gaining FDA approval The source had not heard of any update d launch date yet for Kogenate SF

The source also confirmed that AHP has stated that Refacto® will be available in 3Q00 The source stated without prompting "I'm not sure why American Home sees such a delay in the launch of Refacto® considering it was just approved "

Analyst Comments:

This source was interviewed prior to the analyst discovering that the GI plant in St Louis may not be operational for another two years In a follow-up the analyst requested this source to ask AHP the following during his next company contact

- What is the cause for the delay in bringing St Louis on-line?
- Confirm that the Stockholm Refacto® plant currently has a 250 MAU annual capacity
- Does AHP plan to increase Stockholm's capacity to satisfy demand for Refacto? If so, what will be the new capacity and when?

Senior Product Manager, Global Marketing, Baxter Hyland Immuno

Interview BHI-06

Title. Senior Product Manager, Global Marketing

Organization Baxter Hyland Immuno

Background

This contact has background knowledge on both Kogenate SF and Refacto® and has direct access to information regarding marketing initiatives of the target organizations

Source Comments.

The analyst asked the source about the names of suppliers of equipment and resins for FVIII manufacturing The source referred the analyst for such details to Baxter's manufacturing personnel in Thousand Oaks

The analyst shared with the source the information from NHF that GI's St Louis plant may be delayed another two years The analyst then asked if problems with WFI supply could cause such a delay The source stated that WFI problems could indeed cause delays up to two years

The analyst asked the source where Baxter had originally discovered that the GI plant in Stockholm had an estimated capacity of 250 MAU The source indicated that this information became available during Baxter negotiations with GI in 1997 when rights to Refacto® were up for sale The analyst asked if the source knew of any Baxter personnel involved in these negotiations that were still with Baxter The source indicated two individuals, but noted that they were most likely under some sort of confidentiality agreement with GI

The analyst then asked about the source's knowledge regarding GI s protein free product research The source indicated that Baxter was aware of that GI was developing a protein free product because this was also presented to Baxter in 1997

Regarding possible launch strategies and tactics, the source indicated that she was aware that GI was throwing "lots of promo dollars at NHF" The source noted however, that these dollars were being spent on general research such as a $2 5 million research grant to NHF The source was unaware of any specific promotional programs that either GI or Bayer was initiating through NHF

Regarding pricing, the source noted that Kogenate SF was being priced in Europe the same as the old formulation Kogenate In the case of Refacto®, the source noted that pricing was very close to Recombinate® and other FVIII products

When asked about positioning of either Kogenate SF or Refacto®, the source stated that GI has done a very good job of communicating their peace of mind message of Refacto® as an albumin free formulated product

The discussion then shifted to product enhancements that the source was aware of The source stated that Bayer was looking into improved reconstitution of their product. This could include pre-filled, chambered syringes The source noted that Refacto® originally had a triple chamber syringe, however, Pharmacia & Upjohn kept the rights to the chambered syringe when they sold the rights to Refacto® to GI

The analyst asked the source to provide names of Baxter contacts in Europe and Japan that may be good sources of information for this project The source identified the directors of marketing in Europe and Japan as first points of contact

The source then shifted the conversation to a discussion of the importance of assays in the marketing of Refacto® The source stated that Refacto® requires the use of chromogenic assays to measure FVIII activity in the bloodstream However most clinics use one-stage assays Some physicians object to the use of chromogenic assays as too expensive to establish for one particular product The source noted that this requirement of chromogenic assays with Refacto® could prove to be a considerable

hurdle to effectively marketing the product unless GI is willing, to partially or fully subsidize the establishment of these assays at clinics

Analyst comments.

Due to legal requirements imposed by binding confidentiality agreements, the Baxter personnel involved in negotiations with GI in 1997 could not be interviewed for this project

Senior Marketing Analyst, Baxter Hyland Immuno

Interview. BHI-08

Title. Senior Marketing Analyst

Organization Baxter Hyland Immuno

Background:

This contact is the project lead for this research The analyst contacted her regarding background information on chromogenic assays

Source comments:

The source indicated that Baxter had done marketing research regarding chromogenic assays Essentially, physicians were asked if they were aware that Refacto® required the use of chromogenic assays Many of the surveyed physicians indicated that they were unaware of this assay requirement Many of these physicians further indicated that they objected to adding another assay and its associated costs and training time

The source agreed to contact sources suggested by source BHI-07 for possible interviews

Analyst comments:

The impact of chromogenic assays on the marketability of Refacto® and GI's strategies to deal with practitioner resistance to this will be investigated further under the scope of work area of "Possible launch strategies"

Technical Marketing Manager, Baxter Hyland Immuno

Interview: BHI-09

Title: Technical Marketing Manager

Organization: Baxter Hyland Immuno

Background

This source was contacted for technical background on chromogenic assays

Source comments

The source stated that assays for FVIII are performed at clinics to measure FVIII recovery values The reason given that Refacto® requires chromogenic assays is that one stage assays used with Refacto® can present values that can be off by as much as 50%

This can create a perception barrier as physicians worry about accurate dosage of FVIII since the assay results determine the FVIII dosage level

The main resistance to using chromogenic assays appears to be the start-up costs Although they are less expensive per assay once set-up, chromogenic assays are more expensive to set up and require considerable staff training

To overcome the cost concerns, there is evidence that Wyeth in Europe is giving away all or a portion of chromogenic assay materials to clinics

The analyst then asked the source to assess the current state of the general debate regarding one stage versus chromogenic assays The source indicated that the medical/scientific community is undecided on what is to be the standard assay According to the source "Neither assay is perfect" and this ambivalence fuels the uncertainty in arriving at a single standard

The source stated that scientists at Pharmacia & Upjohn have been very active promoting chromogenic assays as the standard This is not terribly surprising since Pharmacia & Upjohn still retains distribution rights to certain countries for Refacto® and Pharmacia & Upjohn also provides the scientific support for Refacto® For instance, patents for Refacto® upgrades filed since the purchase by American Home Products all list Pharmacia & Upjohn as the filing organization

The topic then shifted to a discussion of a possible two-year delay at GI s St Louis plant The analyst voiced the opinion that this delay was not part of the original launch plan for Refacto® in the U S since the product was already approved for marketing in the U S The source agreed adding that the U S Refacto® approval included an indication for prophylactic administration of Refacto® Although physicians often administer FVIII products prophylacticly for severe hemophilia on an off-label basis to go through the trouble to gain regulatory approval for such an indication hints that the manufacture expected to have a considerable supply This is because prophylactic use of FVIII requires a much greater supply than conventional use of the product

The interview concluded with the source providing some details requested by the analyst (including the former owner of the GI St Louis plant was Chiron and that Baxter had a copy of the deed transfer on this plant from Chiron to AHP)

Analyst comments:

Follow-up research uncovered the address and contact phone number for the GI plant in St Louis Further research will be conducted in an attempt to pin down more precise the delays in a full launch of Refacto® in the U S and likely supply numbers available from Stockholm for the U S market

Director of Operations, Baxter Hyland Immuno

Interview BHI-10

Title Director of Operations

Organization Baxter Hyland Immuno

Background

This source has considerable knowledge of the GI St Louis plant and was interviewed regarding details of the plant's history and possible current status

Source comments

The analyst began by clarifying the source's comments regarding "consistency manufacturing" at the St Louis plant The source had earlier stated informally to the analyst that he had heard that St Louis was in consistency manufacturing in the 4Q99 or 1Q00 The source explained that this information came from a colleague of his who had interviewed for a senior quality assurance position at the St Louis plant in January 1999 The colleague was told by GI interviewers at that time that the St Louis plant would be in consistency manufacturing in either 4Q99 or 1Q00 The source stressed that this information was over one year old and given in an interview, so he was unsure how reliable it is

The source explained that consistency manufacturing is conducted during the very late phase of validation If it is true that the St Louis plant only recently completed consistency manufacturing, it is reasonable to consider the plant to still be two years away from actual commercial production This is due to regulatory hurdles and timelines that any biotech plant of this nature must pass through This delay does not take into account any problems, such as WFI supply difficulties

The source pointed out that there could be nothing mechanically wrong with any of the equipment at St Louis The problem could simply be that, due to the age of the plant,

the equipment was no longer in compliance with current regulations The source explained that biotech plants must be in compliance with current USP guidelines the last one being USP 23 in 1999 Since the St Louis plant has been operating under previous ownership since the early 1980s and since it had been inactive for a considerable period before AHP purchased it, it is quite likely that some of the plant's equipment had not been upgraded to be in compliance with current USP guidelines

If the major problem at St Louis is, in fact, a WFI issue, the source indicated that delivery of a new WFI still can require lead times of 9 months or more and would require validation before it could be used for production

When discussing the issue of supplying the U S Refacto® market from Stockholm the source indicated that this would require the Stockholm plant to file a BLA with the U S FDA

The analyst then asked the source to provide a brief history of ownership of the St Louis plant The source indicated that the first owner was Invitron followed by Monsanto, Centocor, Chiron, and finally, AHP

Finally, the analyst asked the source his views on Wuppertal as a possible location for a second Kogenate SF plant When told that Bayer currently does process development for Kogenate SF at Wuppertal and that Bayer also has a pilot plant there the source stated "Well then, it would be a perfect location, since they have the expertise there but it would be a green [meaning a brand new] site and that would take a long time to bring on line"

Analyst comments:

Other sources are being contacted to confirm that St Louis has completed consistent manufacturing Although the issue of other delays will be explored the analyst's current hypothesis is that the major problems at St Louis were of a regulatory compliance nature that did delay the validation of the plant beyond AHP's original U S launch plan timeline (The current USP guideline document is USP 24, effective January 2000) However, if the plant is confirmed to be past consistency,

manufacturing, it will be assumed that any such problems have been overcome Nonetheless, this would still put the St Louis plant operational start date out to sometime in early 2002

Senior Marketing Analyst, Baxter Hyland Immuno

Interview: BHI-11

Title. Senior Marketing Analyst

Organization Baxter Hyland Immuno

Background

This contact is the project lead for this research She contacted the source with information coming in from the field regarding both Bayer and GI

Source comments:

The source indicated that sources in the Chicago area have heard rumors that GI is considering giving up on the St Louis facility altogether

Regarding a new Kogenate SF plant that Bayer is planning in Europe the source indicated that internal discussion at Baxter speculated that any such plant would take 3-5 years to be operational The source requested that this estimate be confirmed with Baxter manufacturing contacts

Baxter marketing sources have received information that GI is now providing training and equipment for chromogenic assays to clinics requesting this service in North America

Despite these efforts to reduce the cost objection to chromogenic assays Baxter sources in Chicago have heard that certain U S labs are telling treatment centers not to use Refacto® because the labs do not plan to establish a chromogenic assay capability

Baxter sources in Europe are seeing evidence that GI is having difficulty satisfying demand for Refacto® in Europe

Analyst comments.

Baxter manufacturing contacts at Thousand Oaks concurred w th the 3-5 year lead-time estimate for a new biotech plant in Europe

American Home Products indicated to securities analysts durir g the week of March 20, 2000 that their Stockholm Refacto® plant was "maxed out" try ing to meet the European demand for Refacto®

Follow-up interviews are being scheduled with Baxter contact in Chicago and Europe to follow-up on rumors heard at these offices from the field

Supervisor, Permit Service Center, Berkeley, California

Interview BHI-12

Title: Supervisor

Organization: Permit Service Center, Berkeley, California

Background:

Each local municipality has unique procedures for permitting public viewing of permits and drawings for buildings that have filed for permits The analyst contacted this source to discover what the availability and policies were for public viewing of architectural and engineering drawings This contact is a senior supervisor of the building permits and inspection department in Berkeley California Bayer's Kogenate SF® manufacturing facilities are located in two buildings in Berkeley

Source comments·

The source indicated that hard copy architectural and engineering plans are available at the Permit Service Center for buildings still under construction For completed buildings, the Permit Service Center maintains microfilm records of their permits and drawings

The public may view architectural and equipment drawings at the Permit Service Center, however, obtaining copies of the drawings requires permission from Bayer which, according to the source, is unlikely

The permits and drawings for Bayer are contained in one very large file for the main address, 800 Dwight Way The source indicated that if she could be provided some more detailed information, such as the specific building within the Bayer campus that this could expedite research considerably

Analyst comments

The buildings of interest are the original 42,000 square foot Kogenate SF® facility, building 5A, and the new 100,000 square foot Kogenate SF® facility, building 60

The source will be on vacation until Thursday, March 30, 2000 The source will be contacted at that time to work out the logistics involved in reviewing the drawings for these two buildings

Public Information Specialist, Public Works Department, St Louis, Missouri

Interview: BHI-13

Title: Public Information Specialist

Organization: Public Works Department, St Louis Missouri

Background:

The St Louis County Public Works Department provides building inspection services for St Louis and certain surrounding communities in the St Louis area Genetics Institute's manufacturing facility is located in Berkeley, Missouri within St Louis County

Source comments:

The source indicated that the city of Berkeley does not contract inspection services through the St Louis County Public Works Department Therefore any drawings related to a site within Berkeley are likely to be on file with Berkeley's building inspector office

Analyst comments:

A message was left with the Chief Building Inspector of Berkeley Missouri regarding availability and procedures for viewing architectural and engineering drawings on file with the Inspector's office

Director of International Expansion, Intercontinental Region, Baxter Hyland Immuno

Interview: BHI-15

Title: Director of International Expansion, Intercontinental Region

Organization Baxter Hyland Immuno

Background.

This contact had authored a number of internal memos back in 1996 regarding the production capacity of Bayer's Kogenate® manufacturing facility in Berkeley California This interview was conducted to follow-up on some of the information provided in these documents

Source comments

The analyst asked the source about Bayer Kogenate ® capacity calculated at 200MAUs per year in June of 1996 by a now retired Baxter scientist The source indicated that the scientist calculated this from published report on Bayer's bioreactors and yields The source could not recall the title or details of this published report

The source stated that his understanding was that building 60 the new facility at Bayer, was originally designed to produce multiple products, however now it is dedicated to Kogenate SF® production exclusively To the source's knowledge, Bayer uses a continuous perfusion system with hollow-fiber bioreactors at all their production facilities His understanding is that this is the case at GI's plant in Stockholm as well The source noted that hollow-fiber bioreactor suites do not require as large a facility as stirred-tank type suites

When the analyst mentioned GI possibly operating and maximum capacity in Stockholm, the source asked if there might be some stock of bulk Refacto® since the shelf life of bulk FVIII is 3-5 years The analyst indicated that this is unlikely since GI

has already admitted that they are having difficulty meeting demand in Europe alone North America

Analyst comments:

A follow-up interview will be necessary with this contact to clarify some historical information on Bayer's Berkeley site

Director of Government Relations, National Hemophilia Foundation

Interview: BHI-16

Title Director of Government Relations

Organization National Hemophilia Foundation

Background

This source oversees the preparation of NHF's Medical Advisories related to the supply of Factor VIII products The source has regular contact with Factor VIII manufacturers and is kept informed regarding supply issues of these products

In a previous interview, this source indicated that he would be meeting with Bayer sometime this week for an update on the Kogenate SF® launch timeline

Source comments

The source stated that the scheduled meeting with Bayer Corporation marketing personnel was canceled and had not yet been rescheduled

Regarding Refacto®, the source reiterated that marketing personnel at Genetics Institute had indicated that the company was having difficulty satisfying demand in Europe for Refacto® Because of this, Genetics Institute has indicated that they will only divert "a very small amount" to the U S market until a U S manufacturing facility is on line

Analyst comments:

The Refacto® supply problems in Europe have been mentioned by Baxter personnel in Europe, the NHF, and securities analysts (see next interview) This combined with delays in St Louis further indicate a considerable delay before Refacto® can have any real impact on the U S FVIII market

Securities Analyst, Paine Webber

Interview BHI-17

Title: Securities Analyst

Organization: Paine Webber Securities, New York

Background:

This source is a senior biotech analyst at Paine Webber and a covering analyst for AHP The source has indirect information regarding strategic initiatives of AHP and GI The source contacted the analyst following a conference call with AHP during the week of March 20, 2000

Source comments:

During the recent conference call with analysts, AHP U S Investor Relations discussed the status of Refacto® in the U S AHP indicated that it would have adequate supplies of Refacto® going to the U S market by September or October 2000

When asked directly by the source, AHP acknowledged delays at the St Louis facility but gave no details The company went on to state that the delays could push bringing the plant on line for 6-7 months, but that they expected that by 3Q00 everything should be straightened out " The source interpreted this to mean that adequate supplies would be available in the U S by 3Q00, not that the St Louis plant would be operational at that time

Despite AHP's assurances that "everything would be straightened out" by 3Q00 the company also stated that the Stockholm facility was "maxed out" trying to meet demand in Europe The backlog in supplying European demand for Refacto was given as the reason for the delay in supplying the U S market until 3Q00

Analyst comments.

AHP has been very reluctant to supply details of delays in St. Louis to either securities analysts or the NHF. The combination of company statements and information in the field still point to only a token supply of Refacto® in the U.S. market beginning in 3Q00

Vice President, Global Manufacturing, Biotech, Baxter Hyland Division

Interview: BHI-18

Title: Vice President, Global Manufacturing Biotech

Organization Baxter Hyland Division

Background.

This source has worked in biotechnology manufacturing for 13 years and has been instrumental in the establishment of Baxter Hyland's production facility in Thousand Oaks California. The source has also worked as a manufacturing consultant to various biotech manufacturers, including Genetics Institute

The source was contacted to gain insight into some of the information and rumors regarding GI operations in St Louis

Source comments.

The analyst asked the source's reaction to rumors that GI may have decided to start from scratch for a U S Refacto® plant instead of trying to upgrade the St Louis site The source indicated that although he had not visited the St Louis site he was familiar with its design and, in his opinion, it was an over-designed facility that would be very difficult to upgrade to current manufacturing standards

The source stated that he would not be surprised if GI ended up building a new plant at an entirely different site

Regarding Bayer's Kogenate SF® facility, the source stressed that the timing of approval for this facility could be as soon as July if Bayer had already run conformance lots The timing of the approval would also depend on when Bayer submitted data to the FDA on the expansion suite The source suggested contacting regulatory staff a

Baxter in Glendale to determine who at the FDA was responsible for processing such data

The source volunteered information from a Baxter employee in Hayward who had recently left Bayer in Berkeley According to this employee, Bayer is in the midst of a major restructuring of the Berkeley facility The employee stated that Bayer is sending "a lot of Germans" to Berkeley to facilitate the restructuring of the manufacturing management As a result, the employee claims that Bayer is "losing a lot of folks' from the Berkeley location

Analyst comments

Interviews are being scheduled with regulatory staff at Baxter to investigate details of the likely timing of FDA approval for Bayer's new Kogenate SF® facility

The information regarding restructuring at Berkeley matches earlier indications this source had that Bayer was losing people for some reason from the Berkeley facility

Chief Building Inspector, City of Berkeley, Missouri

Interview: BHI-19

Title: Chief Building Inspector

Organization City of Berkeley, Missouri

Background:

Genetics Institute's St Louis manufacturing facility is actually located within the city of Berkeley, Missouri All building permits are submitted and filed at the City of Berkeley's Building Inspection office The analyst contacted this source to discover if and in what format, plans related to the Genetics Institute site were available

Source comments:

The source indicated that any plans related to the Genetics Institute site are in hard copy at the Building Inspection office and can be viewed by the public However the Building Inspection office did not offer any research services The only way to view any plans or drawings related to a building permit is to visit the Building Inspection office in person

Analyst comments:

Unlike larger municipality building inspection offices, Berkeley Missouri does not have an off-site vault storage for older building permit files If Baxter decides it is valuable to see the plans for GI's St Louis facility, there should be little difficulty locating the files and no delays since all files are centrally located

Director of Coagulation Products, Europe and the European Product Manager for Hemophilia, Baxter Hyland Immuno

Interview: BHI-20 and BHI-21

Title: Director of Coagulation Products, Europe
European Product Manager for Hemophilia

Organization Baxter Hyland Immuno

Background.

Both Kogenate SF® and Refacto® are currently approved in Europe These sources have been tracking developments related to the marketing and supply of these products within the European Union

Source Comments

The European Product Manager began the conversation by providing some background information on the market size for FVIII products in Europe The source stated that the EU market contains a total of approximately 36,000 hemophiliacs, including mild cases Of this total, approximately 23,000 are moderate to severe cases

The analyst asked if the EU has any equivalent of the NHF or the Canadian Blood Services tracking the supply of FVIII products in Europe The Director of Coagulation Products indicated that there is no equivalent organization in the EU tracking supply

Regarding regulatory approval of Refacto®, the Director of Coagulation Products stated that the product is approved for marketing throughout the EU except for Belgium, which is expected to approve it within the next two months

Regarding the supply of Refacto® in Europe, the Director of Coagulation Products estimated that AHP was able to supply approximately 90-100 MAUs of Refacto® in 1999 He concurred that the estimated capacity of the Stockholm plant is approximately 250

MAUs He speculated that the difference in supply and capacity was due to either building commercial inventory for the U S market or problems with production at Stockholm

The Director of Coagulation Products had been surprised by the relatively modest start of Refacto® in Europe because AHP claimed to have plenty in stock prior to the European launch However, he noted that during a recent meeting with AHP European marketing personnel, the AHP executives indicated frustration regarding supply issues surrounding both Benefix® and Refacto® This meeting was with an AHP marketing vice president in charge of coagulation products sometime in early February 2000

The analyst then asked the sources if they had heard anything in Europe regarding efforts by AHP to overcome resistance to using chromogenic assays required when administering Refacto® The Director of Coagulation Products stated that only 2 hours previous, he had received information from Baxter's German Sales and Marketing staff that AHP has developed a new standard (reagent) to use with one-stage assays to get accurate equivalent results as in chromogenic assays Baxter Europe has obtained copies of the German brochures related to this and they are translating the copy into English

The Director of Coagulation Products indicated his concern that Kogenate SFS is the more immediate market threat His worst case scenario was that Bayer already has a full-scale dedicated suite producing Kogenate SF® in Berkeley and has stocked significant amounts prior to launch The analyst pointed out that sources in both the U S and Canada had indicated that Bayer originally expected approval of Kogenate SFS by the FDA in the March 2000 The Director of Coagulation Products stated that physician sources in the U K had indicated in 1999 that Kogenate SF® had been originally scheduled for launch in Europe in late 1999 to early 2000, but that there was a delay because production planning had not been in line

Finally, the Director of Coagulation Products asked the analyst to include in the final report any information on Helixate SF®, the private label version of Kogenate SFS

Analyst comments:

None

Supervisor, Permit Service Center, Berkeley, California

Interview: BHI-22

Title: Supervisor, Permit Service Center

Organization: City of Berkeley, California

Background

Bayer's new Kogenate SF® manufacturing facility is located in Berkeley California. Architectural and engineering drawings of this facility and other buildings on Bayer's Berkeley campus are available in hard copy and microfilm at the Permit Service Center. The analyst traveled to Berkeley to review the drawings related to recent work at the Kogenate SF plant. This interview took place during that visit.

Source comments.

The source found the file on the most recent permit, number 3459, regarding the new Kogenate SF® plant. The permit was issued on July 30, 1999. The purpose of the permit was to make piping and HVAC changes to the second and third floors of the plant related to the second bioreactor suite.

The architectural and engineering drawings for this permit were available in hard copy and were provided to the analyst for review. The source then stressed that protocols of the plans could not be made without the permission of the architects.

The drawings included equipment layouts of the fermentation rooms on the second floor as well as general plans of the second and third floors of the facility. The first page of the drawings included a general plan of the Bayer campus as of July 1999.

Analyst comments:

The analyst reviewed earlier drawings of Bayer's Berkeley facility that were on microfilm Through this review, the analyst was able to identify the functior of many of the buildings on the campus

The analyst then made tracings of the critical portions of the drawings of the third and second floor o[the facility The analyst also made a sketch of the entire campus identifying key productior, R&D, and warehousing facilities

Formal drawings will be developed from the traces and sketches made during this visit Also, the information gathered from the Permit Service Center will be combined with earlier information gathered from a product video presentation made by Bayer at the International Society on Thrombosis and Hemostasis back in August 1999 The combined information will be presented to Baxter manufacturing personnel to make a reasonable estimate of Bayer's current and projected Kogenate SF® capacity

Investor Relations Manager, Genetics Institute

Interview. BHI-23

Title: Investor Relations Manager

Organization: Genetics Institute

Background:

On April 4, 2000 AHP announced that the company was building a new biotech facility in the Republic of Ireland The analyst took this opportunity to contact GI directly to gather information on how this may impact manufacturing plans in St Louis

Source comments:

When asked if the building of the Ireland plant would have any impact on GI s plans for St. Louis, the source gave a flat "no comment"

Analyst comments:

This brief conversation is included so as to inform Baxter of the likely reaction from different departments within GI Obviously, Investor Relations at GI is much less forthcoming than other departments contacted

Assistant VP for Hemophilia Products, Global Strateg c Marketing, Genetics Institute

Interview: BHI-24

Title. Assistant VP for Hemophilia Products, Glob.l Strategic Marketing

Organization Genetics Institute

Background.

This source has direct access to information regarding marketing plans for Refacto® He was contacted by the analyst as follow-up to the April 4, 2000 a.nouncement of the AHP biotech plant in Ireland

Source comments:

The source referred the analyst to GI's communications departmen regarding manufacturing plans in St Louis

However, in the course of clarifying his current job title, the source volunteered that GI restructured its management organization beginning approximatel y two months ago Now the company is organized into eight therapeutic areas As a result of the restructuring, the source is both the VP for Hemophilia Products and the head of the Hemophilia Therapeutic Area.

Analyst comments·

Interview BHI-25 was conducted with the source in the Corr munications Department referred to by this contact

Assistant VP of North American Communications, American Home Products

Interview: BHI-25

Title: Assistant VP of North American Communications

Organization American Home Products

Background:

This source has indirect access to information regarding marketing and manufacturing plans for Refacto® He was contacted as a follow-up to the AHP announcement on April 4 2000 regarding the building of a new biotech manufacturing facility in the Republic of Ireland

Source comments.

The analyst asked the source if the Republic of Ireland facility is intended to supply Refacto® globally or the European market only The source stated that the intention is that the Ireland plant would supply Refacto® globally

The analyst then asked if the building of the Ireland plant would have any impact on Baxter's plans for their St Louis facility The source responded that "No, that [St Louis] is moving ahead as planned" The analyst pointed out that the Ireland facility is planned to be operational in 2004 The source was then asked, in light of the 2004 date for Ireland, when St Louis was scheduled to be operational The source indicated that St Louis is scheduled to be operational by the end of 2000 or early 2001 The analyst asked if this meant that the FDA would approve the St Louis facility at this time or if the plant would simply be ready for validation at that point The source was uncertain, but committed to finding out further details

Analyst comments

If it turns out that the St Louis plant is only going to be operational and not approved by the FDA by the end of 2000, this would be consistent with earlier information that it will not be producing Refacto® for the U S market for two years after 1999

VP Corporate Communications, Genetics Institute

Source. BHI-26

Title. VP Corporate Communications

Organization Genetics Institute

Background·

This source heads up the communications function for Genetics Institute The source has indirect access to information regarding marketing and manufacturing decisions on Refacto®

Source comments

The source claimed to be unaware that GI had a manufacturing facility in St Louis The source referred such detailed questions to the Assistant VP of North American Communications or the Assistant VP of International Communications at AHP

Analyst comments:

The analyst had by this time, already interviewed the Assistant VP of North American Communications in interview BHI-25

If true, this source's claim that he had no knowledge of the St Louis plant indicates that he is a poor source for any future detailed inquiries regarding manufacturing operations The Assistant VP of North American Communications appeared to be quite knowledgeable regarding these types of details It is recommended that the VP of Corporate Communications not be contacted in the future Such contact would most likely reveal the new information while possibly alerting senior management to the inquiries

Plant Manager, Genetics Institute, Berkeley (St Louis), Missouri

Interview BHI-27

Title. Plant Manager

Organization Genetics Institute

Background:

This source is the plant manager for Genetics Institute's planned Refacto® manufacturing facility in St Louis County, Missouri This source has direct access to information regarding the plans and regulatory status of this facility

Source comments.

The analyst began the conversation by stating that this interview was a follow-up to AHP's April 4, 2000 announcement regarding the building of a biotech manufacturing facility in the Republic of Ireland The analyst pointed out that AHP indicated in the press release that the Ireland facility was due to be operational by 2004 The analyst then asked in light of the Ireland plant being operational in 2004, when was the St Louis plant due to be operational? The source indicated that he could not comment on such details, and referred the analyst back to Genetics Institute headquarters in New Jersey

Analyst comments:

This interview is included only to inform Baxter that this plant manager is not a viable source for useful information

Director of Operations, Baxter Hyland Immuno

Interview: BHI-28

Title: Director of Operations

Organization: Baxter Hyland Immuno, Thousand Oaks California

Background

This source had a recent conversation with a Baxter operations manager in Switzerland who is in contact with individuals that were involved with process development for Kogenate SF® During this face-to-face interview, engineering drawings of building 60 at Baxter's Berkeley facility were reviewed and left with this source

Source comments:

The source indicated that from what he understood from Baxter in Switzerland the new Bayer plant's bioreactors were 25 times denser than those used in Baxter's plant in Thousand Oaks What this means in practical terms is that each 200 liter bioreactor at Berkeley is roughly equivalent in production to one 2000 liter bioreactor at Baxter's Thousand Oaks facility

However, due to the limitations of the raw material used in the production of Kogenate SF® (BHK cells), the actual capacity would be somewhat less than that of a 2000 liter bioreactor

The source noted that Bayer had spent two years in developing the manufacturing process for Kogenate SF®, utilizing high-density cell culture technology

The source closed the interview by providing the analyst with contact information for Baxter's operations manager in Switzerland

Analyst comments:

If this source s information is correct, Bayer's facility in Berkeley would have a maximum theoretical capacity of 1000 MAU per year At minimum, it should be able to reach a capacity of 750 MAU per year.

Director of Global Public Policy and Communications, Bayer Corporation

Interview: BHI-29

Title. Director of Global Public Policy and Communications

Organization· Bayer Corporation, Raleigh, North Carolina

Background.

This source has direct access to information regarding the capacity of Bayer's Kogenate SF® manufacturing facility in Berkeley, California

Source comments

The source indicated that the "new technology" deployed at Bayer's Berkeley facility significantly increases yields from the same amount of source material in each 200-liter fermenter This translates into a capacity that will eventually double the capacity of Berkeley

The analyst then asked when Bayer expected U S approval of Kogenate SF® The source indicated that Bayer expected U S FDA approval of Kogenate SF® sometime in 2H00

Finally, the analyst asked if Bayer was continuing to produce the old formulation of Kogenate® The analyst pointed out that there had been conflicting reports in this regard some indicating that Bayer had stopped production of Kogenate® in December 1999 while other reports indicated that Bayer was still producing the product The source stated that Bayer intended to continue to produce Kogenate® until the company gained FDA approval of Kogenate SF®

Analyst comments

This interview contains the most accurate estimated U S Kogerate SF® approval date so far It also is the first direct company confirmation that Bayer is continuing to manufacture Kogenate®

Assistant Director, Los Angeles Office, Irish Development Authority

Interview: BHI-30

Title: Assistant Director, Los Angeles Office

Organization Irish Development Authority

Background:

The Irish Development Authority (IDA) provides information and other assistance to foreign business operating in the Republic of Ireland The source was contacted to collect information regarding the issue of commercial building permits in the Republic of Ireland

Source comments:

The source indicated that for commercial properties, the owner must submit detailed architectural and engineering drawings to the planning department of the local authority at the city or county council level Also, any planned commercial building owner must publish their intentions in a prominent newspaper within the affected area to allow for any public objections If there are objections, an appeal goes before a review board called in Gaelic "An Bord Pleanala"

Once the permits are granted, the permits, along with any associated drawings and correspondence, are kept on file with the local planning department as public records

Analyst comments:

It appears that the requirements for building permits in Ireland are essentially the same as those in the U S Once a permit is issued to AHP in County Dublin for their new manufacturing facility at Grange Castle, the drawings and other documents will be available to the public at the local planning department with responsibility for Grange Castle

Irish Consulate General, San Francisco, California

Interview: BHI-31

Title. Information desk

Organization Irish Consulate General, San Francisco, California

Background

An investigation of secondary sources by the analyst discovered that in 1994, County Dublin was broken up into three different county councils The analyst contacted the Irish Consulate General to discover which new county council was responsible for Grange Castle

Source comments

The source at the desk was uncertain, however another consulate staff person was familiar with Grange Castle and indicated that the county council responsible for this area was the Dundrum County Council

Source comments

When permits are issued for the AHP manufacturing plant in Ireland, it is advisable that someone contact or visit the planning department at Dundrum, Republic of Ireland A telephone call will be enough to verify that engineering plans are available for the AHP plant at Grange Castle The file may also be under the name Wyeth-Lederle or Wyeth-Medica

BDS Program Manager, Baxter Hyland, Switzerland

Interview: BHI-32

Title: BDS Program Manager

Organization. Baxter Hyland, Switzerland

Background:

This source is a former colleague of an individual who was directly involved in the process development for Kogenate SF® Previous to this interview the analyst saw scale engineering drawings of Bayer's Kogenate SF®

Source comments:

The source indicated that the manufacturing process for Kogenate SF® incorporates a cell retention device that concentrates cells in the bioreactor This technology is new and different from that used in the manufacture of the original Kogenate® Bayer developed this process over at least a two-year period The result is a process that is 10 times more productive than that used in conventional bioreactors This means that one 200-liter bioreactor is roughly the equivalent of one 2000 liter conventional bioreactor

The source reiterated the point made by Baxter's U S Director of Operations that the BHK cell line is not as good as CHO cells in expressing desirable proteins However the source had the opinion that Bayer has used some if its process development time to improve the performance of the BHK cells they use in manufacturing

The interview closed with the source providing the names of two individuals involved in the process development of Kogenate SF®

Analyst comments.

This source effectively confirmed that the Bayer Berkeley facil ty will have an ultimate theoretical capacity of 1000 MAUs, but a real world capacity tna is somewhat less due to limitations of the BHK cell line

Assistant Vice President International Communications, American Home Products

Interview. BHI-33

Title: Assistant Vice President International Communications

Organization: American Home Products

Background:

This source has indirect access to information regarding regulatory approval of Refacto® in markets outside North America.

Source comments:

The source indicated that the regulatory filing for Refacto® in Japan is being managed by Yamanouchi Pharmaceuticals, who has the marketing rights to the product in Japan. The source was uncertain regarding the target approval date for Japan.

The source indicated that AHP currently had no target dates for approval of Refacto® in either Australia or New Zealand.

Analyst comments:

For more details on the status of Refacto® in Japan will require liaison with Baxter personnel in Japan and/or interviews with analysts covering Yamanouchi Pharmaceuticals in considerable detail. A review of analyst reports on Yamanouchi revealed no mention of Refacto®.

Vice President, Global Manufacturing, Biotech, Baxter Hyland Immuno

Interview: BHI-34

Title: Vice President, Global Manufacturing, Biotech

Organization Baxter Hyland Immuno

Background

This source was contacted regarding projected capacities and approval dates for Baxter manufacturing facilities in Thousand Oaks California and Neuchatel Switzerland

Source comments

The source indicated that when all three suites are operational at Thousand Oaks, this facility would have a capacity ranging from 750-825 MAU per year The source expected to have full approval for all three suites from the FDA sometime in 4Q00

Regarding Neuchatel, the source indicated that there would be 4 suites of 2 bioreactors each at this location (for a total of 8 bioreactors) The total capacity at Neuchatel is projected to be 1000 MAU per year for production of the protein-free product, or 750 MAU per year producing the current formulation of Recombinate®

Regarding Neuchatel, the source stated that his last information was that Neuchatel was targeted for full production by 3Q03 if clinical studies are required for the protein-free product However, the source recommended that the analyst check with Baxter personnel in Glendale, California to verify this information

Analyst comments

The analyst conducted a follow-up interview with a Baxter manager in Glendale as recommended by this source

Director, Global Public Policy and Communications, Bayer Corporation

Interview: BHI-35

Title: Director, Global Public Policy and Communications

Organization: Bayer Corporation, Raleigh, North Carolina

Background:

This source has direct access to information regarding regulatory approval dates for Kogenate SF®

Source comments:

Regarding regulatory approval of Kogenate SF® in Japan, the source indicated that Bayer is targeting a date sometime in 2001, but he had nothing more specific than that. Regarding Australia, the source stated that Bayer hopes to gain approval there sometime in 4Q00. The source stated that regulatory approval in Australia is tied to approval in the U.S. which is scheduled for the 2H00. Finally, the source stated that Kogenate SF® was approved in New Zealand in the 4Q99.

Analyst comments

None

Controller, Recombinant Products, Baxter Hyland Immuno

Interview: BHI-36

Title: Controller, Recombinant Products

Organization Baxter Hyland Immuno

Background:

This interview was conducted on the advice of Baxter's Vice President of Global Manufacturing to verify target dates for Baxter's manufacturing facility in Neuchatel Switzerland

Source comments

The source stated that Neuchatel is scheduled to conduct conformance production runs of protein-free product for clinical studies in 4Q00 Full licensing of the Neuchatel plant by the FDA is targeted for 3Q02 EU approval of the Neuchatel facility is targeted for 4-6 months following FDA approval

Analyst comments.

None

---End of Interviews---

Re FVIII - Global

Mfg Capacity

Update

RECOMBINANT FACTOR VIII GLOBAL MANUFACTURING CAPACITY UPDATE NOVEMBER 2000

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November 2000 Page

RECOMBINANT FACTOR VIII GLOBAL MANUFACTURING CAPACITY

EXECUTIVE SUMMARY

This research was conducted in late October 2000 verify and update rFVIII manufacturing capacity estimates contained in a previous competitive intelligence report prepared in June 2000 for Baxter Hyland Immuno The objective of this follow-up research was to estimate the current and potential manufacturing capacity for Bayer's Kogenate FS® and Genetics Institute's Refacto®